6

Carbanions and Other Carbon Nucleophiles

Introduction

This chapter is concerned with carbanions, which are the conjugate bases (in the Brønsted sense) formed by deprotonation at carbon atoms. Carbanions are very important in synthesis because they are good nucleophiles and formation of new carbon-carbon bonds often requires a nucleophilic carbon species. Carbanions vary widely in stability, depending on the hybridization of the carbon atom and the ability of substituent groups to stabilize the negative charge. In the absence of a stabilizing substituent, removal of a proton from a C–H bond is difficult. There has therefore been much effort devoted to study of the methods of generating carbanions and understanding substituent effects on stability and reactivity. Fundamental aspects of carbanion structure and stability were introduced in Section 3.4.2. In this chapter we first consider the measurement of hydrocarbon acidity. We then look briefly at the structure of organolithium compounds, which are important examples of carbanionic character in organometallic compounds. In Section 6.3 we study carbanions that are stabilized by functional groups, with emphasis on carbonyl compounds. In Section 6.4 the neutral nucleophilic enols and enamines are considered. Finally in Section 6.5 we look at some examples of carbanions as nucleophiles in S_N2 reactions.

6.1. Acidity of Hydrocarbons

In the discussion of the relative acidity of carboxylic acids in Chapter 1 (p. 53–54), the thermodynamic acidity, expressed as the acid dissociation constant in aqueous solution, was taken as the measure of acidity. Determining the dissociation constants of carboxylic acids in aqueous solution by measuring the titration curve with a pH-sensitive electrode is straightforward, but determination of the acidity of hydrocarbons is more difficult. As most are quite weak acids, very strong bases are required

to effect deprotonation. Water and alcohols are far more acidic than nearly all hydrocarbons and are unsuitable solvents for the generation of anions from hydrocarbons. Any strong base will deprotonate the solvent rather than the hydrocarbon. For synthetic purposes, aprotic solvents such as diethyl ether, THF, and DME are used, but for equilibrium measurements solvents that promote dissociation of ion pairs and ion clusters are preferred. Weakly acidic solvents such as dimethyl sulfoxide (DMSO) and cyclohexylamine are used in the preparation of strongly basic carbanions. The high polarity and cation-solvating ability of DMSO facilitates dissociation of ion pairs so that the equilibrium data refer to the solvated dissociated ions, rather than to ion aggregates.

The basicity of a base-solvent system can be specified by a basicity function H_-. The value of H_- corresponds essentially to the pH of strongly basic nonaqueous solutions. The larger the value of H_-, the greater the proton-abstracting ability of the medium. The process of defining a basicity function is analogous to that described for acidity functions in Section 3.7.1.3. Use of a series of overlapping indicators permits assignment of H_- values to base-solvent systems, and allows pK's to be determined over a range of 0–35 pK units.[1] The indicators employed include substituted anilines and arylmethanes that have significantly different electronic (UV–VIS) spectra in their neutral and anionic forms. Table 6.1 presents H_- values for some representative solvent-base systems.

The acidity of a hydrocarbon can be determined in an analogous way.[2] If the electronic spectra of the neutral and anionic forms are sufficiently different, the concentration of each can be determined directly in a solution of known H_-; the equilibrium constant for

$$RH + B^- \rightleftharpoons R^- + BH$$

is related to pK_{RH} by the equation

$$pK_{RH} = H_- + \log \frac{[RH]}{[R^-]} \tag{6.1}$$

Table 6.1. Values of H_- for Some Representative Solvent-Base Systems

Solution	H_-[a]
1 *M* KOH	14.0
5 *M* KOH	15.5
10 *M* KOH	17.0
1.0 *M* NaOMe in MeOH	17.0
5.0 *M* NaOMe in MeOH	19.0
0.01 *M* NaOMe in 1:1 DMSO-MeOH	15.0
0.01 *M* NaOMe in 10:1 DMSO-MeOH	18.0
0.01 *M* NaOEt in 20:1 DMSO-EtOH	21.0

a. Selected values from J. R. Jones, *The Ionization of Carbon Acids*, Academic Press, New York, 1973, Chap. 6, are rounded to the nearest 0.5 pH unit.

1. We will restrict the use of pK_a to acid dissociation constants in aqueous solution. The designation pK refers to the acid dissociation constant under other conditions.
2. D. Dolman and R. Stewart, *Can. J. Chem.*, **45**, 911 (1967); E. C. Steiner and J. M. Gilbert, *J. Am. Chem. Soc.*, **87**, 382 (1965); K. Bowden and R. Stewart, *Tetrahedron*, **21**, 261 (1965).

When the acidities of hydrocarbons are compared in terms of the relative stabilities of neutral and anionic forms, the appropriate data are *equilibrium* acidity measurements, which relate directly to the relative stability of the neutral and anionic species. For compounds with pK > ~35, it is difficult to obtain equilibrium data. In such cases, it may be possible to compare the *rates of deprotonation*, i.e., the *kinetic acidity.* These comparisons can be made between different protons in the same compound or between two different compounds by following an isotopic exchange. In the presence of a deuterated solvent, the rate of incorporation of deuterium is a measure of the rate of carbanion formation.[3] Tritium (^{3}H)-NMR spectroscopy is also a sensitive method for direct measurement of kinetic acidity.[4]

$$\begin{aligned} RH + B^- &\rightleftharpoons R^- + BH \\ R^- + SD &\rightleftharpoons RD + S^- \\ S^- + BH &\rightleftharpoons SH + B^- \end{aligned}$$

It has been found that there is often a correlation between the rate of proton abstraction (kinetic acidity) and the thermodynamic stability of the carbanion (thermodynamic acidity). Owing to this relationship, kinetic measurements can be used to extend scales of hydrocarbon acidities. These kinetic measurements have the advantage of not requiring the presence of a measurable concentration of the carbanion; instead, the relative ease of carbanion formation is judged by the rate at which exchange occurs. This method is applicable to weakly acidic hydrocarbons for which no suitable base will generate a measurable carbanion concentration.

The kinetic method of determining relative acidity suffers from one serious complication, however, which has to do with the fate of the ion pair that is formed immediately on abstraction of the proton.[5] If the ion pair separates and diffuses rapidly into the solution, so that each deprotonation results in exchange, the exchange rate is an accurate measure of the rate of deprotonation. Under many conditions of solvent and base, however, an ion pair may return to reactants at a rate exceeding protonation of the carbanion by the solvent, a phenomenon known as *internal return*.

$$R_3C{-}H + M^+B^- \underset{\text{internal return}}{\overset{\text{ionization}}{\rightleftharpoons}} [R^3C^-M^+ + BH] \xrightarrow{\text{dissociation}} R_3C^- + M^+ + BH$$

$$R_3C^- \xrightarrow{SD\ \text{exchange}} R_3CD + S^-$$

When there is internal return, a deprotonation event escapes detection because exchange does not occur. One experimental test for the occurrence of internal return is racemization at chiral carbanionic sites that takes place without exchange. Even racemization cannot be regarded as an absolute measure of the deprotonation rate because, under some conditions, hydrogen-deuterium exchange has been shown to occur with retention of configuration. Owing to these uncertainties about the fate of ion pairs, it is important

[3] A. I. Shatenshtein, *Adv. Phys. Org. Chem.*, **1**, 155 (1963).

[4] R. E. Dixon, P. G. Williams, M. Saljoughian, M. A. Long, and A. Streitwieser, *Magn. Res. Chem.*, **29**, 509 (1991); A. Streitwieser, L. Xie, P. Speers, and P. G. Williams, *Magn. Res. Chem.*, **36**, S 209 (1998).

[5] W. T. Ford, E. W. Graham, and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 4661 (1967); D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 3688 (1961).

that a linear relationship between exchange rates and equilibrium acidity be established for representative examples of the compounds under study. A satisfactory correlation provides a basis for using kinetic acidity data for compounds of that structural type.

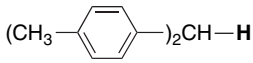
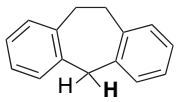
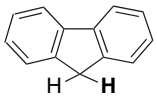
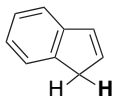
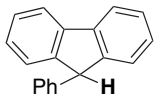
The nature of the solvent in which the extent or rate of deprotonation is determined has a significant effect on the apparent acidity of the hydrocarbon. In general, the extent of ion aggregation is primarily a function of the ability of the solvent to solvate the ionic species. In THF, DME, and other ethers, there is usually extensive ion aggregation. In dipolar aprotic solvents, especially dimethyl sulfoxide, ion pairing is less significant.[6] The identity of the cation also has a significant effect on the extent of ion pairing. Hard cations promote ion pairing and aggregation. Because of these factors, the numerical pK values are not absolute and are specific to the solvent and cation. Nevertheless, they provide a useful measure of relative acidity. The two solvents that have been used for most quantitative measurements on hydrocarbons are dimethyl sulfoxide and cyclohexylamine.

A series of hydrocarbons has been studied in cyclohexylamine, using cesium cyclohexylamide as base. For many of the compounds studied, spectroscopic measurements were used to determine the relative extent of deprotonation of two hydrocarbons and thus establish relative acidity.[7] For other hydrocarbons, the acidity was derived by kinetic measurements. It was shown that the rate of tritium exchange for a series of related hydrocarbons is linearly related to the equilibrium acidities of these hydrocarbons in the solvent system. This method was used to extend the scale to hydrocarbons such as toluene for which the exchange rate, but not equilibrium data, can be obtained.[8] Representative values of some hydrocarbons with pK values ranging from 16 to above 40 are given in Table 6.2. The pK values of a wide variety of organic compounds have been determined in DMSO,[9] and some of these values are listed in Table 6.2 as well. It is not expected that these values will be numerically identical with those in other solvents, but for most compounds the same relative order of acidity is observed. For synthetic purposes, carbanions are usually generated in ether solvents, often THF or DME. There are relatively few quantitative data available on hydrocarbon acidity in such solvents. Table 6.2 contains a few entries for Cs^+ salts. The numerical values are scaled with reference to the pK of 9-phenylfluorene.[10] The acidity trends are similar to those in cyclohexylamine and DMSO.

Some of the relative acidities in Table 6.2 can be easily understood. The order of decreasing acidity $Ph_3CH > Ph_2CH_2 > PhCH_3$, for example, reflects the ability of each successive phenyl group to stabilize the negative charge on carbon. This stabilization is a combination of both resonance and the polar EWG effect of the phenyl groups. The much greater acidity of fluorene relative to dibenzocycloheptatriene (Entries 5 and 6) is the result of the aromaticity of the cyclopentadienide ring in the anion of fluorene. Cyclopentadiene (Entry 9) is an exceptionally acidic hydrocarbon, comparable in acidity to simple alcohols, owing to the aromatic stabilization of the anion. Some more subtle effects are seen as well. Note that fusion of a benzene ring *decreases* the acidity

6. E. M. Arnett, T. C. Moriarity, L. E. Small, J. P. Rudolph, and R. P. Quirk, *J. Am. Chem. Soc.*, **95**, 1492 (1973); T. E. Hogen-Esch and J. Smid, *J. Am. Chem. Soc.*, **88**, 307 (1966).
7. A. Streitwieser, Jr., J. R. Murdoch, G. Hafelinger, and C. J. Chang, *J. Am. Chem. Soc.*, **95**, 4248 (1973); A. Streitwieser, Jr., E. Ciuffarin, and J. H. Hammons, *J. Am. Chem. Soc.*, **89**, 63 (1967); A. Streitwieser, Jr., E. Juaristi, and L. L. Nebenzahl, in *Comprehensive Carbanion Chemistry*, Part A, E. Buncel and T. Durst, ed., Elsevier, New York, 1980, Chap. 7.
8. A. Streitwieser, Jr., M. R. Granger, F. Mares, and R. A. Wolf, *J. Am. Chem. Soc.*, **95**, 4257 (1973).
9. F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).
10. D. A. Bors, M. J. Kaufman, and A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **107**, 6975 (1985).

Table 6.2. Acidity of Some Hydrocarbons

Entry	Hydrocarbon	Cs^+ (CHA)[a]	Cs^+ (THF)[b]	K^+ (DMSO)[c]
1	$PhCH_2$—**H**	41.2	40.9	43
2		35.1	33.1	
3	$(Ph_2)CH$—**H**	33.4	33.3	32.3
4	$(Ph)_3C$—**H**	31.4	31.3	30.6
5		31.2		
6		22.7	22.9	22.6
7		19.9		20.1
8		18.5	18.2	17.9
9		16.6		18.1

a. A Streitwieser, Jr., J. R. Murdoch, G. Hafelinger, and C. J. Chang, *J. Am. Chem. Soc.*, **93**, 4248 (1973); A. Streitwieser, Jr., E. Ciuffarin, and J. H. Hammons, *J. Am. Chem. Soc.*, **89**, 93 (1967); A. Streitwieser, Jr., and F. Guibe, *J. Am. Chem. Soc.*, **100**, 4523 (1978).
b. M. J. Kaufman, S. Gronert, and A. Streitwieser, *J. Am. Chem. Soc.*, **110**, 2829 (1988); A. Streitwieser, J. C. Ciula, J. A. Krom, and G. Thiele, *J. Org. Chem.*, **56**, 1074 (1991).
c. F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456, 463 (1988).

of cyclopentadiene, as illustrated by comparing Entries 6, 7, and 9. (This relationship is considered in Problem 6.3)

Allylic conjugation stabilizes carbanions and pK values of 43 (in cyclohexylamine)[11] and 47–48 (in THF-HMPA)[12] were determined for propene. On the basis of exchange rates with cesium cyclohexylamide, cyclohexene and cycloheptene were found to have pK values of about 45 in cyclohexylamine.[13] These data indicate that allylic positions have p$K \sim 45$. The hydrogens on the sp^2 carbons in benzene and ethene are more acidic than the hydrogens in saturated hydrocarbons. A pK of 45 has been estimated for benzene on the basis of extrapolation from a series of halogenated

11. D. W. Boerth and A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **103**, 6443 (1981).
12. B. Jaun, J. Schwarz, and R. Breslow, *J. Am. Chem. Soc.*, **102**, 5741 (1980).
13. A. Streitwieser, Jr., and D. W. Boerth, *J. Am. Chem. Soc.*, **100**, 755 (1978).

benzenes.[14] Electrochemical measurements have been used to establish a lower limit of about 46 for the pK of ethene.[12]

For saturated hydrocarbons, exchange is too slow and reference points are so uncertain that determination of pK values by exchange measurements is not feasible. The most useful approach for obtaining pK data for such hydrocarbons involves making a measurement of the electrochemical potential for the reaction:

$$R\cdot + e^- \rightarrow R^-$$

From this value and known C–H bond dissociation energies, we can calculate the pK values. Early application of these methods gave estimates of the pK of toluene of about 45 and of propene of about 48. Methane was estimated to have a pK in the range of 52–62.[12] Electrochemical measurements in DMF have given the results in Table 6.3.[15] These measurements put the pK of methane at about 48, with benzylic and allylic stabilization leading to values of 39 and 38 for propene and toluene, respectively. These values are several units smaller than those determined by other methods. The electrochemical values overlap with the pK_{DMSO} scale for compounds such as diphenylmethane and triphenylmethane, and these values are also somewhat lower than those found by equilibrium studies.

Terminal alkynes are among the most acidic of the hydrocarbons. For example, in DMSO, phenylacetylene is found to have a pK near 26.5.[16] In cyclohexylamine, the value is 23.2.[17] An estimate of the pK in aqueous solution of 20 is based on a Brønsted relationship (see p. 348).[18] The relatively high acidity of acetylenes is associated with the large degree of *s* character of the C–H bond. The *s* character is 50%, as opposed to 25% in sp^3 bonds. The electrons in orbitals with high *s* character experience decreased shielding from the nuclear charge. The carbon is therefore effectively *more electronegative*, as viewed from the proton sharing an *sp* hybrid orbital, and hydrogens on *sp* carbons exhibit greater acidity. (See Section 1.1.5 to review carbon hybridization-electronegativity relationships.) This same effect accounts for the relatively high acidity

Table 6.3. pK Values for Less Acidic Hydrocarbons

Hydrocarbon	pK(DMF)[a]
Methane	48
Ethane	51
Cyclopentane	49
Cyclohexane	49
Propene	38
Toluene	39
Diphenylmethane	31
Triphenylmethane	29

a. K. Daasbjerg, *Acta Chem. Scand.*, **49**, 878 (1995).

14. M. Stratakis, P. G. Wang, and A. Streitwieser, Jr., *J. Org. Chem.*, **61**, 3145 (1996).
15. K. Daasbjerg, *Acta Chem. Scand.*, **49**, 878 (1995).
16. F. G. Bordwell and W. S. Matthews, *J. Am. Chem. Soc.*, **96**, 1214 (1974).
17. A. Streitwieser, Jr., and D. M. E. Reuben, *J. Am. Chem. Soc.*, **93**, 1794 (1971).
18. D. B. Dahlberg, M. A. Kuzemko, Y. Chiang, A. J. Kresge, and M. F. Powell, *J. Am. Chem. Soc.*, **105**, 5387 (1983).

of the hydrogens on cyclopropane rings and other strained hydrocarbons that have increased *s* character in the C–H bonds. The relationship between hybridization and acidity can be expressed in terms of the *s* character of the C–H bond.[19]

$$pK_a = 83.1 - 1.3(\%s)$$

The correlation can also be expressed in terms of the NMR coupling constant J^{13}C–H, which is related to hybridization.[20] These numerical relationships break down when applied to a wider range of molecules, where other factors contribute to carbanion stabilization.[21]

Knowledge of the structure of carbanions is important to understanding the stereochemistry of their reactions. Ab initio (HF/4-31G) calculations indicate a pyramidal geometry at carbon in the methyl and ethyl anions. The optimum H–C–H angle in these two carbanions is calculated to be 97°–100°. An interesting effect is found in that the proton affinity (basicity) of methyl anion decreases in a regular manner as the H–C–H angle is decreased.[22] This increase in acidity with decreasing internuclear angle parallels the trend in small-ring compounds, in which the acidity of hydrogens is substantially greater than in compounds having tetrahedral geometry at carbon. Pyramidal geometry at carbanions can also be predicted on the basis of qualitative considerations of the orbital occupied by the unshared electron pair. In a planar carbanion, the lone pair would occupy a *p* orbital. In a pyramidal geometry, the orbital has more *s* character. Because the electron pair is of lower energy in an orbital with some *s* character, it is predicted that a pyramidal geometry will be favored. Qualitative VSEPR considerations also predict pyramidal geometry (see p. 7).

As was discussed in Section 3.8, measurements in the gas phase, which eliminate the effect of solvation, show structural trends that parallel measurements in solution but have much larger absolute energy differences. Table 6.4 gives some data for key hydrocarbons for the ΔH of proton dissociation. These data show a correspondence with

Table 6.4. Enthalpy of Proton Dissociation for Some Hydrocarbons (Gas Phase)[a]

Hydrocarbon	ΔH(kcal/mol)[a]
Methane	418.8
Ethene	407.5
Cyclopropane	411.5
Benzene	400.8
Toluene	381

a. S. T. Graul and R. R. Squires, *J. Am. Chem. Soc.*, **112**, 2517 (1990).

19. Z. B. Maksic and M. Eckert-Maksic, *Tetrahedron*, **25**, 5113 (1969); M. Randic and Z. Maksic, *Chem. Rev.*, **72**, 43 (1972).
20. A. Streitwieser, Jr., R. A. Caldwell, and W. R. Young, *J. Am. Chem. Soc.*, **91**, 529 (1969); S. R. Kass and P. K. Chou, *J. Am. Chem. Soc.*, **110**, 7899 (1988); I. Alkorta and J. Elguero, *Tetrahedron*, **53**, 9741 (1997).
21. R. R. Sauers, *Tetrahedron*, **55**, 10013 (1999).
22. A. Streitwieser, Jr., and P. H. Owens, *Tetrahedron Lett.*, 5221 (1973); A. Steitwieser, Jr., P. H. Owens, R. A. Wolf, and J. E. Williams, Jr., *J. Am. Chem. Soc.*, **96**, 5448 (1974); E. D. Jemmis, V. Buss, P. v. R. Schleyer, and L. C. Allen, *J. Am. Chem. Soc.*, **98**, 6483 (1976).

hybridization and delocalization effects observed in solution. The very large heterolytic dissociation energies reflect both the inherent instability of the carbanions and the electrostatic attraction between the oppositely charged carbanion and proton. By way of comparison, enthalpy measurements in DMSO using $K^{+}\cdot{}^{-}O$-*t*-Bu or KCH_2SOCH_3 as base give values of −15.4 and −18.2 kcal/mol, respectively, for fluorene, a hydrocarbon with a p*K* of about 20.[23]

Aqueous phase acidity for a number of hydrocarbons has been computed theoretically. A continuum dielectric solvation model was used and B3LYP/6-311++G(*d*, *p*) and MP2/G2 computations were employed.[24] Some of the results are given in Table 6.5 There is good agreement with experimental estimates for most of the compounds, although cyclopropane is somewhat less acidic than anticipated.

Tupitsyn and co-workers dissected the energies of deprotonation into two factors—the C–H bond energy and the structural reorganization of the carbanion—by calculating the energy of the carbanion at the geometry of the reactant hydrocarbon and then calculating the energy of relaxation to the minimum energy structure using AM1 computations.[25] It was found that strained ring compounds were dominated by the first factor, whereas compounds such as propene and toluene that benefit from carbanion delocalization were dominated by the second term. Benzene has a very low relaxation energy, consistent with a carbanion localized in an sp^2 orbital. The broad general picture that emerges from this analysis is that there are two major factors that influence the acidity of hydrocarbons. One is the inherent characteristics of the C–H bond resulting from hybridization and strain and the other is anion stabilization, which depends on delocalization of the charge.

The stereochemistry observed in proton exchange reactions of carbanions is dependent on the conditions under which the anion is formed and trapped by proton transfer. The dependence on solvent, counterion, and base is the result of the importance of ion pairing effects. The base-catalyzed cleavage of **1** is illustrative. The anion of **1** is cleaved at elevated temperatures to 2-butanone and 2-phenyl-2-butyl anion, which under the conditions of the reaction is protonated by the solvent. Use of resolved

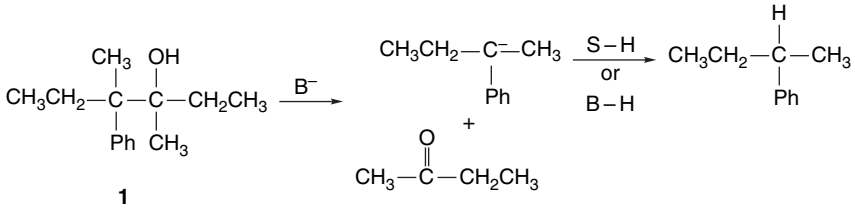
Table 6.5. Computed Aqueous p*K* Values for Some Hydrocarbons

Hydrocarbon	B3LYP	MP2/G2
Ethyne	24.7	25.1
Cyclopentadiene	17.8	19.1
Cyclopropane	52.2	52.3
Toluene	42.1	42.4
Ethane	53.8	55.0

a. I. A. Topol, G. J. Tawa, R. A. Caldwell, M. A. Eisenstad, and S. K. Burt, *J. Phys. Chem. A*, **104**, 9619 (2000).

23. E. M. Arnett and K. G. Venkatasubramanian, *J. Org. Chem.*, **48**, 1569 (1983).
24. I. A. Topol, G. J. Tawa, R. A. Caldwell, M. A. Eisenstat, and S. K. Burt, *J. Phys. Chem. A*, **104**, 9619 (2000).
25. I. F. Tupitsyn, A. S. Popov, and N. N. Zatsepina, *Russian J. Gen. Chem.*, **67**, 379 (1997).

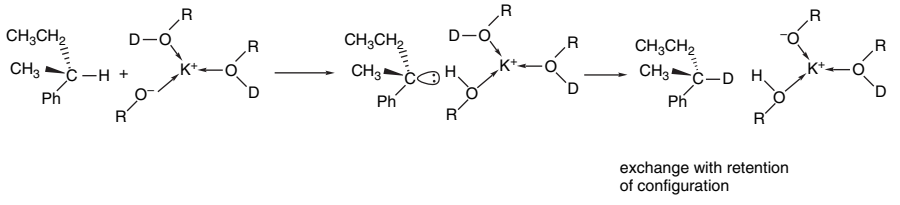
1 allows the stereochemical features of the anion to be probed by measuring the enantiomeric purity of the 2-phenylbutane product.



1

Retention of configuration was observed in nonpolar solvents, while increasing amounts of inversion occurred as the proton-donating ability and the polarity of the solvent increased. Cleavage of **1** with potassium *t*-butoxide in benzene gave 2-phenylbutane with 93% net retention of configuration. The stereochemical course changed to 48% net inversion of configuration when potassium hydroxide in ethylene glycol was used. In DMSO using $K^+ \cdot {}^-O$-*t*-Bu as base, completely racemic 2-phenylbutane was formed.[26] The retention in benzene presumably reflects a short lifetime for the carbanion in a tight ion pair. Under these conditions, the carbanion does not become symmetrically solvated before proton transfer from either the protonated base or the ketone. The solvent benzene is not an effective proton donor and the most likely proton source is *t*-butanol. In ethylene glycol, the solvent provides a good proton source and since net inversion is observed, the protonation must occur on an unsymmetrically solvated species that favors back-side protonation. The racemization that is observed in DMSO indicates that the carbanion has a sufficient lifetime to become symmetrically solvated. The stereochemistry observed in the three solvents is in good accord with their solvating properties. In benzene, reaction occurs primarily through ion pairs. Ethylene glycol provides a ready source of protons and fast proton transfer accounts for the observed inversion. DMSO promotes ion pair dissociation and equilibration, as indicated by the observed racemization.

The stereochemistry of hydrogen-deuterium exchange at the chiral carbon in 2-phenylbutane shows a similar trend. When potassium *t*-butoxide is used as the base, the exchange occurs with retention of configuration in *t*-butanol, but racemization occurs in DMSO.[27] The retention of configuration is visualized as occurring through an ion pair in which a solvent molecule coordinated to the metal ion acts as the proton donor. In DMSO, symmetrical solvation is achieved prior to protonation and there is complete racemization.



[26.] D. J. Cram, A. Langemann, J. Allinger, and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 5740 (1959).
[27.] D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 3688 (1961).

6.2. Carbanion Character of Organometallic Compounds

The organometallic derivatives of lithium, magnesium, and other strongly electropositive metals have some of the properties expected for salts of carbanions. Owing to the low acidity of most hydrocarbons, organometallic compounds usually cannot be prepared by proton transfer reactions. Instead, the most general preparative methods start with the corresponding halogen compound.

$$CH_3I + 2Li \longrightarrow CH_3Li + LiI$$

$$CH_3(CH_2)_3Br + Mg \longrightarrow CH_3(CH_2)_3MgBr$$

$$PhBr + 2Li \longrightarrow PhLi + LiBr$$

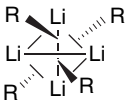
There are other preparative methods, which are considered in Chapter 7 of Part B.

Organolithium compounds derived from saturated hydrocarbons are extremely strong bases and react rapidly with any molecule having an −OH, −NH, or −SH group by proton transfer to form the hydrocarbon. Accurate pK values are not known, but range upward from the estimate of ~50 for methane. The order of basicity $CH_3Li < CH_3(CH_2)_3Li < (CH_3)_3CLi$ is due to the electron-releasing effect of alkyl substituents and is consistent with increasing reactivity in proton abstraction reactions in the order $CH_3Li < CH_3(CH_2)_3Li < (CH_3)_3CLi$. Phenyl- , methyl, *n*-butyl- , and *t*-butyllithium are all stronger bases than the anions of the hydrocarbons listed in Table 6.2. Unlike proton transfers from oxygen, nitrogen, or sulfur, proton removal from carbon atoms is usually not a fast reaction. Thus, even though *t*-butyllithium is thermodynamically capable of deprotonating toluene, the reaction is quite slow. In part, the reason is that the organolithium compounds exist as tetramers, hexamers, and higher aggregates in hydrocarbon and ether solvents.[28]

In solution, organolithium compounds exist as aggregates, with the degree of aggregation depending on the structure of the organic group and the solvent. The nature of the species present in solution can be studied by low-temperature NMR. *n*-Butyllithium in THF, for example, is present as a tetramer-dimer mixture.[29] The tetrameric species is dominant.

$$[(BuLi)_4\cdot(THF)_4] + 4\ THF \rightleftharpoons 2\ [(BuLi)_2\cdot(THF)_4]$$

Tetrameric structures based on distorted cubic structures are also found for $(CH_3Li)_4$ and $(C_2H_5Li)_4$,[30] and they can be represented as tetrahedral of lithium ions with each face occupied by a carbanion ligand.



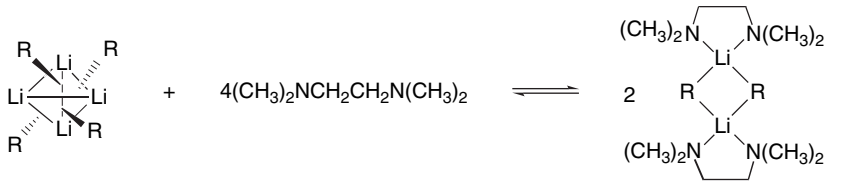
[28] G. Fraenkel, M. Henrichs, J. M. Hewitt, B. M. Su, and M. J. Geckle, *J. Am. Chem. Soc.*, **102**, 3345 (1980); G. Fraenkel, M. Henrichs, M. Hewitt, and B. M. Su, *J. Am. Chem. Soc.*, **106**, 255 (1984).

[29] D. Seebach, R. Hassig, and J. Gabriel, *Helv. Chim. Acta*, **66**, 308 (1983); J. F. McGarrity and C. A. Ogle, *J. Am. Chem. Soc.*, **107,** 1805 (1984).

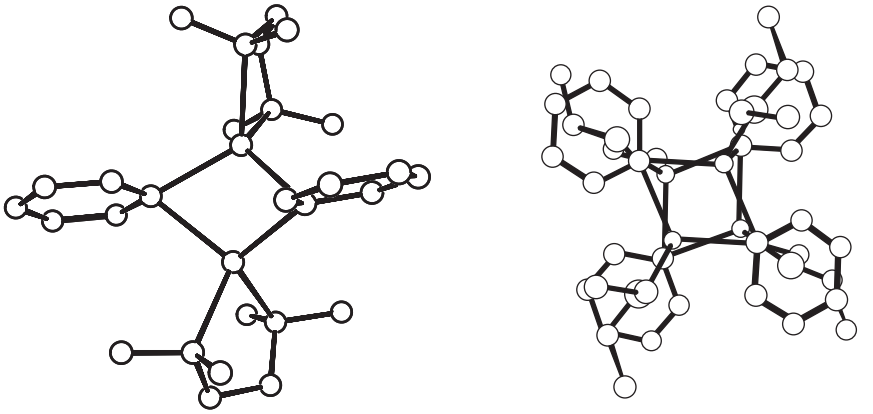
[30] E. Weiss and E. A. C. Lucken, *J. Organomet. Chem.*, **2**, 197 (1964); E. Weiss and G. Hencken, *J. Organomet. Chem.*, **21**, 265 (1970); H. Koester, D. Thoennes, and E. Weiss, *J. Organomet. Chem.*, **160**, 1 (1978); H. Dietrich, *Acta Crystallogr.*, **16**, 681 (1963); H. Dietrich, *J. Organomet. Chem.*, **205**, 291 (1981).

The THF solvate of lithium *t*-butylacetylide is another example of a tetrameric structure.[31] In solutions of *n*-propyllithium in cyclopropane at 0°C, the hexamer is the main species, but higher aggregates are present at lower temperatures.[20]

The reactivity of the organolithium compounds is increased by adding molecules capable of solvating the lithium cations. Tetramethylenediamine (TMEDA) is commonly used for organolithium reagents. This tertiary diamine can chelate lithium. The resulting complexes generally are able to effect deprotonation at accelerated rates.[32] In the case of phenyllithium, NMR studies show that the compound is tetrameric in 1:2 ether-cyclohexane, but dimeric in 1:9 TMEDA-cyclohexane.[33]



X-ray crystal structure determinations have been done on both dimeric and tetrameric structures. A dimeric structure crystallizes from hexane containing TMEDA.[34] This structure is shown in Figure 6.1a. A tetrameric structure incorporating four ether molecules forms from ether-hexane solution.[35] This structure is shown in Figure 6.1b. There is a good correspondence between the structures that crystallize and those indicated by the NMR studies.



(A) $[(PhLi)_2(TMEDA)_2]$ (B) $[(PhLi)_4(Et_2O)_4]$

Fig. 6.1. Crystal structures of phenyllithium: (a) dimeric structure incorporating tetramethylethylenediamine; (b) tetrameric structure incorporating diethyl ether. Reproduced from *Chem. Ber.*, **111**, 3157 (1978) and *J. Am. Chem. Soc.*, **105**, 5320 (1983), by permission of Wiley-VCH and the American Chemical Society, respectively.

31. W. Neuberger, E. Weiss, and P. v. R. Schleyer, quoted in Ref. 37.
32. G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); R. West and P. C. Jones, *J. Am. Chem. Soc.*, **90**, 2656 (1968).
33. L. M. Jackman and L. M. Scarmoutzos, *J. Am. Chem. Soc.*, **106**, 4627 (1984).
34. D. Thoennes and E.Weiss, *Chem. Ber.*, **111**, 3157 (1978).
35. H. Hope and P. P. Power, *J. Am. Chem. Soc.*, **105**, 5320 (1983).

Crystal structure determination has also been done on several complexes of *n*-butyllithium. A 4:1 *n*-BuLi:TMEDA complex is a tetramer accommodating two TMEDA molecules, which, rather than chelating a lithium, links the tetrameric units. The 2:2 *n*-BuLi:TMEDA complex has a structure similar to $[PhLi]_2$:$[TMEDA]_2$. Both 1:1 *n*-BuLi:THF and 1:1 *n*-BuLi:DME complexes are tetrameric with ether molecules coordinated at each lithium (Figure 6.2).[36] These and many other organolithium structures have been discussed in a review of this topic.[37]

There has been extensive computational study of the structure of organolithium compounds.[38] The structures of the simple monolithium compounds are very similar to the corresponding hydrocarbons. The gas phase structure of monomeric methyllithium has been determined to be tetrahedral with an H–C–H bond angle of 106°.[39] These structural parameters are close to those calculated at the MP2/6-311G* level of theory.[40] Ethyllithium, and vinyllithium are also structurally similar to the corresponding

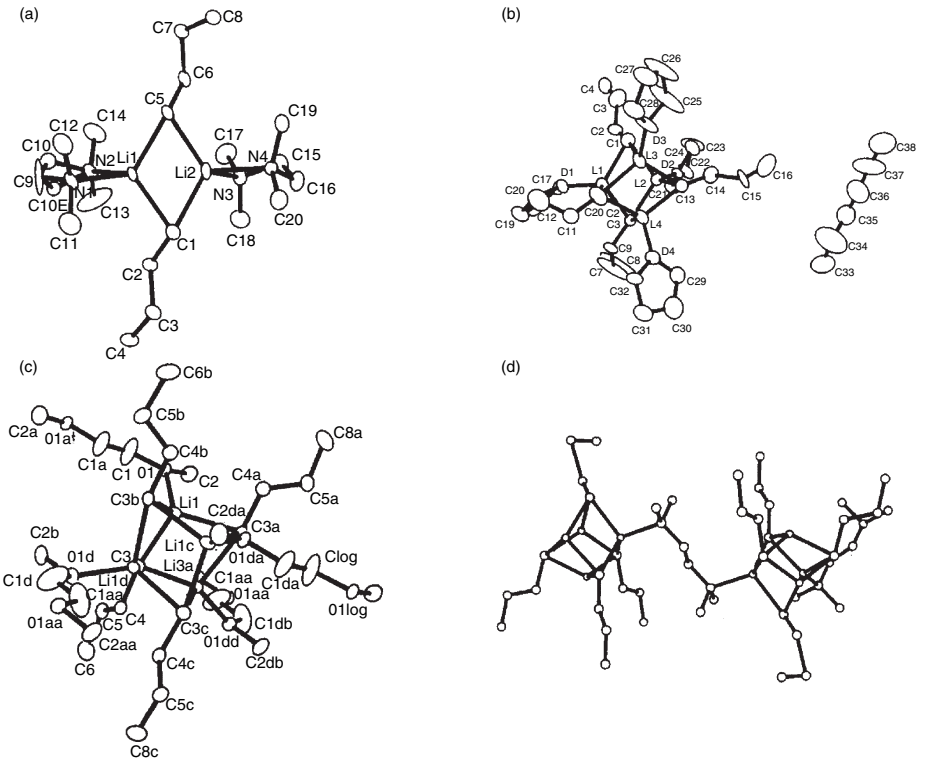


Fig. 6.2. Crystal structures of *n*-butyllithium: (a) [(*n*−BuLi·TMEDA)$_2$]; (b) [(*n*-BuLi·THF)$_4$hexane]; (c) [(*n*-BuLi·DME)$_4$] ; (d) [(*n*-BuLi)$_4$.TMEDA]. Reproduced from *J. Am. Chem. Soc.*, **115**, 1568, 1573 (1993), by permission of the American Chemical Society.

36. M. A. Nichols and P. G. Williard, *J. Am. Chem. Soc.*, **115**, 1568 (1993); N. D. R. Barnett, R. E. Mulvey, W. Clegg, and P. A. O'Neil, *J. Am. Chem. Soc.*, **115**, 1573 (1993).
37. W. N. Setzer and P. v. R. Schleyer, *Adv. Organomet. Chem.*, **24**, 353 (1985).
38. A. Streitwieser, S. M. Bachrach, A. Dorigo, and P. v. R. Schleyer, in *Lithium Chemistry*, A. M. Sapse and P. v. R. Schleyer, eds., Wiley, New York, 1995, pp. 1–43.
39. D. B. Grotjahn, T. C. Pesch, J. Xin, and L. M. Ziurys, *J. Am. Chem. Soc.*, **119**, 12368 (1997).
40. E. Kaufman, K. Raghavachari, A. E. Reed, and P. v. R. Schleyer, *Organometallics*, **7**, 1597 (1988).

hydrocarbon. This fact, along with the relatively high solubility of simple lithium compounds in nonpolar solvents, has given rise to the idea that the C–Li bond is largely covalent. However, AIM analysis of simple alkyllithium compounds indicates that the bonds are largely ionic. The charges on lithium in methyl- and vinyllithium are $+0.91e$ and $+0.92e$, respectively.[41] The ionic character is also evident in the structure of allyllithium. The lithium is centered above the allyl anion, indicating an ionic structure.[42] The good solubility in nonpolar solvents is perhaps due to the cluster-type structures, which place the organic groups on the periphery of the cluster.

The relative slowness of the abstraction of protons from carbon acids by organolithium reagents is probably also due to the compact character of the carbon-lithium clusters. Since the electrons associated with the carbanion are tightly associated with the cluster of lithium cations, some activation energy is required to break the bond before the carbanion can act as a base. This kinetic sluggishness of organometallic compounds as bases permits important reactions in which the organometallic species acts as a *nucleophile* in preference to functioning as a strong base. The addition reactions of organolithium and organomagnesium compounds to carbonyl groups in aldehydes, ketones, and esters are important examples. As will be seen in the next section, carbonyl compounds are much more acidic than hydrocarbons. Nevertheless, in most cases, the proton transfer reaction of organometallic reagents is *slower than nucleophilic attack at the carbonyl group*. It is this feature of the reactivity of organometallics that permits the very extensive use of organometallic compounds in organic synthesis. The reactions of organolithium and organomagnesium compounds with carbonyl compounds is discussed in a synthetic context in Chapter 7 of Part B.

6.3. Carbanions Stabilized by Functional Groups

Electron-withdrawing substituents cause very large increases in the acidity of C–H bonds. Among the functional groups that exert a strong stabilizing effect on carbanions are carbonyl, nitro, sulfonyl, and cyano. Both polar and resonance effects are involved in the ability of these functional groups to stabilize the negative charge. Perhaps the best basis for comparing these groups is the data on the various substituted methanes. Bordwell and co-workers determined the relative acidities of the substituted methanes with reference to aromatic hydrocarbon indicators in DMSO.[43] The data are given in Table 6.6, which established the ordering $NO_2 > C{=}O > CO_2R \sim SO_2 \sim CN > CONR_2$ for anion stabilization.

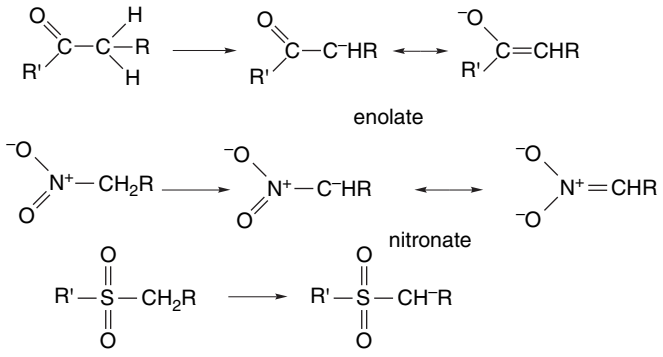
Carbanions derived from carbonyl compounds are often referred to as *enolates*, a name derived from the enol tautomer of carbonyl compounds. The resonance-stabilized enolate anion is the conjugate base of both the keto and enol forms of carbonyl compounds. The anions of nitro compounds are called *nitronates* and are also resonance stabilized. The stabilization of anions of sulfones is believed to be derived primarily from polar and polarization effects.

41. J. P. Richie and S. M. Bachrach, *J. Am. Chem. Soc.*, **109**, 5909 (1987).
42. T. Clark, C. Rohde, and P. v. R. Schleyer, *Organometallics*, **2**, 1344 (1983).
43. F. G. Bordwell and W. S. Matthews, *J. Am. Chem. Soc.*, **96**, 1216 (1974); W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 7006 (1975).

Table 6.6. Equilibrium Acidities of Substituted Methanes in Dimethyl Sulfoxide[a]

Compound	p*K*
CH_3NO_2	17.2
CH_3COPh	24.7
CH_3COCH_3	26.5
CH_3SO_2Ph	29.0
$CH_3CO_2C_2H_5$	30.5[b]
$CH_3SO_2CH_3$	31.1
CH_3CN	31.3
$CH_3CON(C_2H_5)_2$	34.5[b]

a. Except as noted otherwise, from W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G.J McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 7006 (1975).
b. F. G. Bordwell and H. E. Fried, *J. Org. Chem.*, **46**, 4327 (1981).

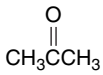
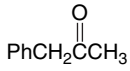
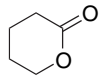
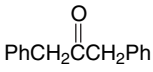
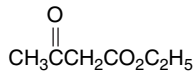
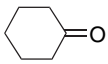
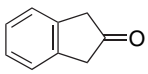
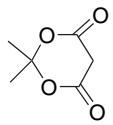
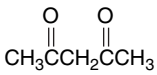
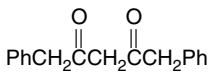
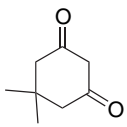
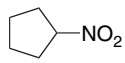
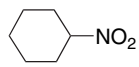


The presence of two EWGs further stabilizes the negative charge. Pentane-2,4-dione, for example, has a p*K* around 9 in water. Most ß-diketones are sufficiently acidic that their carbanions can be generated using the conjugate bases of hydroxylic solvents such as water or alcohols, which have p*K* values of 15–20. Stronger bases are required for compounds that have a single stabilizing functional group. Alkali metal salts of ammonia or amines and sodium hydride are sufficiently strong bases to form carbanions from most ketones, aldehydes, and esters. The Li^+ salt of diisopropylamine (LDA) is a popular strong base for use in synthetic procedures. It is prepared by reaction of *n*-BuLi with diisopropylamine. Lithium, sodium, and potassium salts of hexamethyldisilylamide (LiHMDS, NaHMDS, KHMDS) are also important.[44] The generation of carbanions stabilized by electron-attracting groups is very important from a synthetic point of view; the synthetic aspects of the chemistry of these carbanions is discussed in Chapters 1 and 2 of Part B. Table 6.7 gives experimental p*K* data for some representative compounds in DMSO.

There have been numerous studies of the rates of deprotonation of carbonyl compounds. These data are of interest not only because they define the relationship

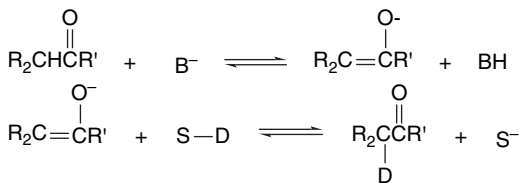
[44.] T. L. Rathman, *Spec. Chem. Mag.*, **9**, 300 (1989).

Table 6.7. p*K* Values for Other Representative Compounds in DMSO[a]

Ketones	p*K*	Esters	p*K*
	26.5	$PhCH_2CO_2C_2H_5$	22.6
	24.7	$PhSCH_2CO_2C_2H_5$	21.4
	19.9		25.2
	18.7	Ketoesters	
	25.8		14.2
	26.4	Diesters	
	16.95	$CH_2(CO_2C_2H_5)_2$	16.4
Diketones			7.3
	13.3	Nitroalkanes	
	13.35	CH_3NO_2	17.2
		$PhCH_2NO_2$	12.3
	11.2		16.0
			17.9

a. F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).

between thermodynamic and kinetic acidity for these compounds, but also because they are necessary for understanding mechanisms of reactions in which enolates are involved as intermediates. Rates of enolate formation can be measured conveniently by following isotopic exchange using either deuterium or tritium.



An older technique is to measure the rate of halogenation of the carbonyl compound. Ketones and aldehydes in their carbonyl forms do not react rapidly with the halogens but the enolate is rapidly attacked. The rate of halogenation is therefore a measure of the rate of deprotonation.

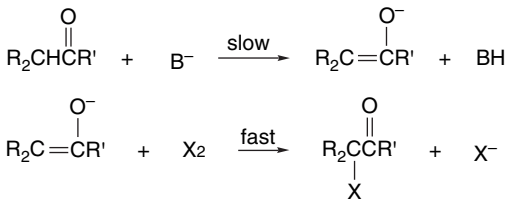


Table 6.8 gives data on the rates of deuteration of some alkyl ketones. From these data, the order of reactivity toward deprotonation is $CH_3 > RCH_2 > R_2CH$. Steric hindrance to the approach of the base is the major factor in establishing this order. The importance of steric effects can be seen by comparing the CH_2 group in 2-butanone with the more hindered CH_2 group in 4,4-dimethyl-2-pentanone. The two added methyl groups on the adjacent carbon decrease the rate of proton removal by a factor of about 100. The rather slow rate of exchange at the CH_3 group of 4,4-dimethyl-2-pentanone must also reflect a steric factor arising from the bulky nature of the neopentyl group. If bulky groups

Table 6.8. Relative Rates and E_a for Base-Catalyzed Deuteration of Some Ketones

Ketone	Relative Rate[a]	E_a[b]
CH_3CCH_2—**H**	100	11.9
CH_3CCHCH_3 (**H**)	41.5	12.1
H—$CH_2CCH_2CH_3$	45	
$CH_3CC(CH_3)_2$ (**H**)	<0.1	
H—$CH_2CCH(CH_3)_2$	45	12.3
$CH_3CCHC(CH_3)_3$ (**H**)	0.45	
H—$CH_2CCH_2C(CH_3)_3$	5.1	

a. In aqueous solution with sodium carbonate as the base. The data of C. Rappe and W. H. Sachs, *J. Org. Chem.*, **32**, 4127 (1967), given on a per-group basis have been converted to a per-hydrogen basis.

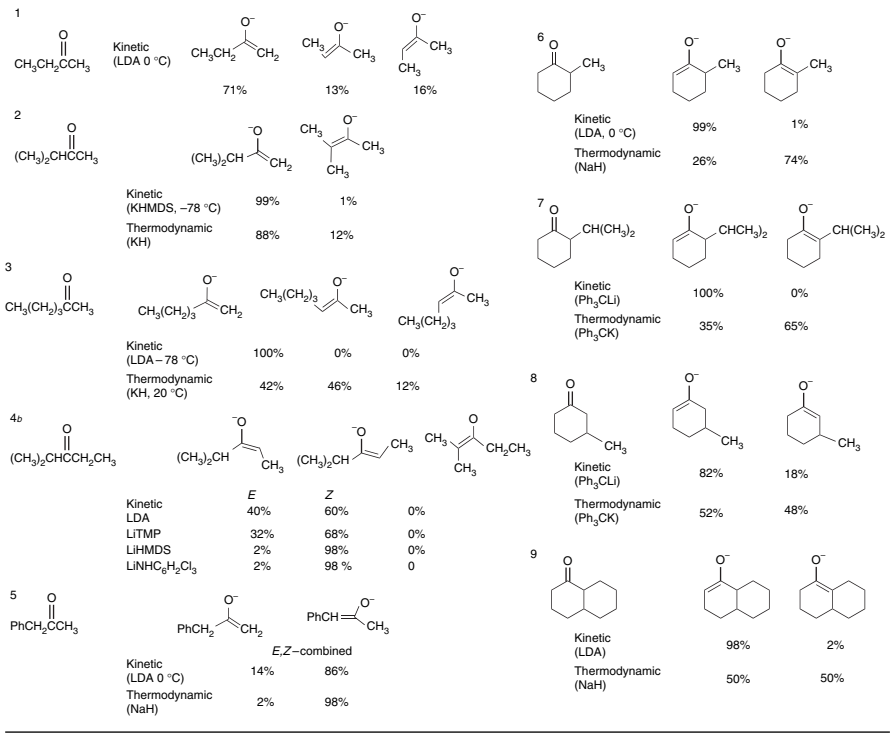
b. CH_3O^--catalyzed exchange in CH_3OD. T. Niya, M. Yukawa, H. Morishita, H. Ikeda, and Y. Goto, *Chem. Pharm. Bull.*, **39**, 2475 (1991).

interfere with effective solvation of the developing negative charge on oxygen, the rate of proton abstraction is reduced. The observed activation energies parallel the rates.[45]

Structural effects on the rates of deprotonation of ketones have also been studied using very strong bases under conditions where complete conversion to the enolate occurs. In solvents such as THF or DME, bases such as LDA and KHMDS give solutions of the enolates that reflect the relative rates of removal of the different protons in the carbonyl compound (*kinetic control*). The least hindered proton is removed most rapidly under these conditions, so for unsymmetrical ketones the major enolate is the less-substituted one. Scheme 6.1 shows some representative data. Note that for many ketones, both *E*- and *Z*-enolates can be formed.

The equilibrium ratios of enolates for several ketone-enolate systems are also shown in Scheme 6.1. Equilibrium among the various enolates of a ketone can be established by the presence of an excess of the ketone, which permits reversible proton transfer. Equilibration is also favored by the presence of dissociating additives such as HMPA. As illustrated by most of the examples in Scheme 6.1, the kinetic enolate is formed by removal of the least hindered hydrogen. The composition of the equilibrium enolate mixture is usually more closely balanced than for kinetically

Scheme 6.1. Composition of Enolate Mixtures Formed under Kinetic and Thermodynamic Control[a]



a. Selected from a more complete compilation by D. Caine, in *Carbon-Carbon Bond Formation*, R. L. Augustine, ed., Marcel Dekker, New York, 1979.
b. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980); L. Xie, K van Landeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.*, **68**, 641 (2003).

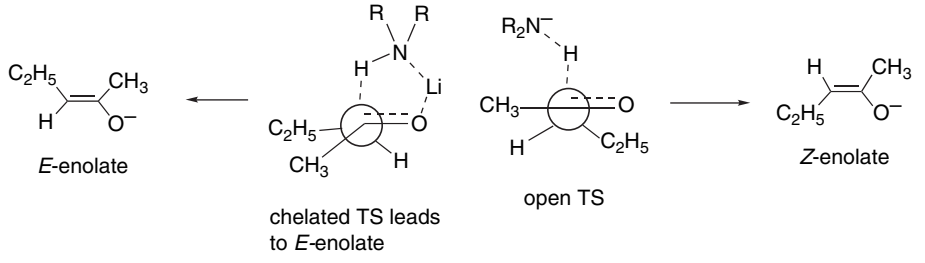
45. T. Niiya, M. Yukawa, H. Morishita, H. Ikeda, and Y. Goto, *Chem. Pharm. Bull.*, **39**, 2475 (1991).

controlled conditions. In general, the more highly substituted enolate is the preferred isomer, but if the alkyl groups are sufficiently branched as to interfere with solvation of the enolate there are exceptions. This factor, along with CH_3/CH_3 repulsion, presumably accounts for the higher stability of the less-substituted enolate from 3-methyl-2-butanone (Entry 2). The acidifying effect of an adjacent phenyl group outweighs steric effects in the case of 1-phenyl-2-propanone, and as a result the conjugated enolate is favored by both kinetic and thermodynamic conditions (Entry 5).

The synthetic importance of the LDA and LiHMDS type of deprotonation has led to studies of enolate composition under various conditions. Deprotonation of 2-pentanone was examined with LDA in THF, with and without HMPA. C(1)-deprotonation was favored under both conditions, but the *Z*:*E* ratio for C(3) deprotonation was sensitive to the presence of HMPA (0.75 *M*).[46] More *Z*-enolate is formed when HMPA is present.

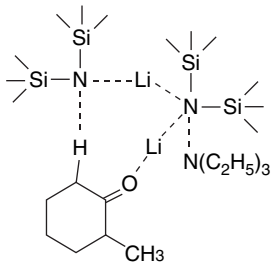
Conditions	Ratio C(1):C(3) deprotonation	Ratio *Z*:*E* for C(3) deprotonation
0°C, THF alone	7.9	0.20
−60°C, THF alone	7.1	0.15
0°C, THF – HMPA	8.0	1.0
−60°C, THF – HMPA	5.6	3.1

These and other related enolate ratios are interpreted in terms of a tight, reactant-like TS with Li chelation in THF and a looser TS in the presence of HMPA. The chelated TS favors the *E*-enolate, whereas the open TS favors the *Z*-enolate. The effect of the HMPA is to solvate the Li^+ ion, reducing the importance of Li^+ coordination with the carbonyl oxygen.[47]

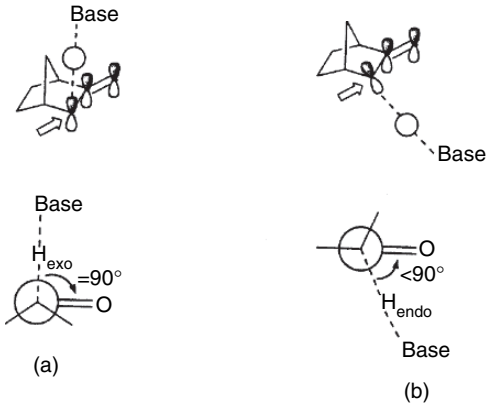


Very significant acceleration of the rate of deprotonation of 2-methylcyclohexanone by LiHMDS was observed when triethylamine was included in enolate-forming reactions in toluene. The rate enhancement is attributed to a TS containing LiHMDS dimer and triethylamine. This is an example of how modification of conditions can be used to affect rates and selectivity of deprotonation.

46. L. Xie and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **113**, 3123 (1991).
47. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1972); R. E. Ireland, P. Wipf, and J. D. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).



Structural effects on deprotonation rates have also been probed computationally.[48] In cyclic ketones, a stereoelectronic factor can be important in determining the rate of deprotonation. For the norbornanone ring, for example, the *exo* proton is more favorably aligned with the carbonyl group than the *endo* hydrogen. Computational investigation (B3LYP/6-31G*) of the TS for deprotonation by an $OH^-:H_2O$ complex found a difference of 3.8 kcal/mol favoring *exo* deprotonation.



A similar factor is found for deprotonation of cyclohexanone. There is a 2.8 kcal preference for removal of an axial proton because of the better stereoelectronic alignment and less torsional strain, as depicted in Figure 6.3.

Nitroalkanes show an interesting relationship between kinetic and thermodynamic acidity. Additional alkyl substituents on nitromethane retard the rate of proton removal, although the equilibrium is more favorable for the more highly substituted derivatives.[49] The alkyl groups have a strong stabilizing effect on the nitronate ion but unfavorable steric effects are dominant at the TS for proton removal. As a result, kinetic and thermodynamic acidity show opposite responses to alkyl substitution.

Nitroalkane	Kinetic acidity $k(M^{-1}\text{min}^{-1})$	Thermodynamic acidity (pK_a)
CH_3NO_2	238	10.2
$CH_3CH_2NO_2$	39.1	8.5
$(CH_3)_2CHNO_2$	2.08	7.7

48. S. M. Behnam, S. E. Benham, K. Ando, N. S. Green, and K. N. Houk, *J. Org. Chem.*, **65**, 8970 (2000).
49. F. G. Bordwell, W. J. Boyle, Jr., and K. C.Yee, *J. Am. Chem. Soc.*, **92**, 5926 (1970).

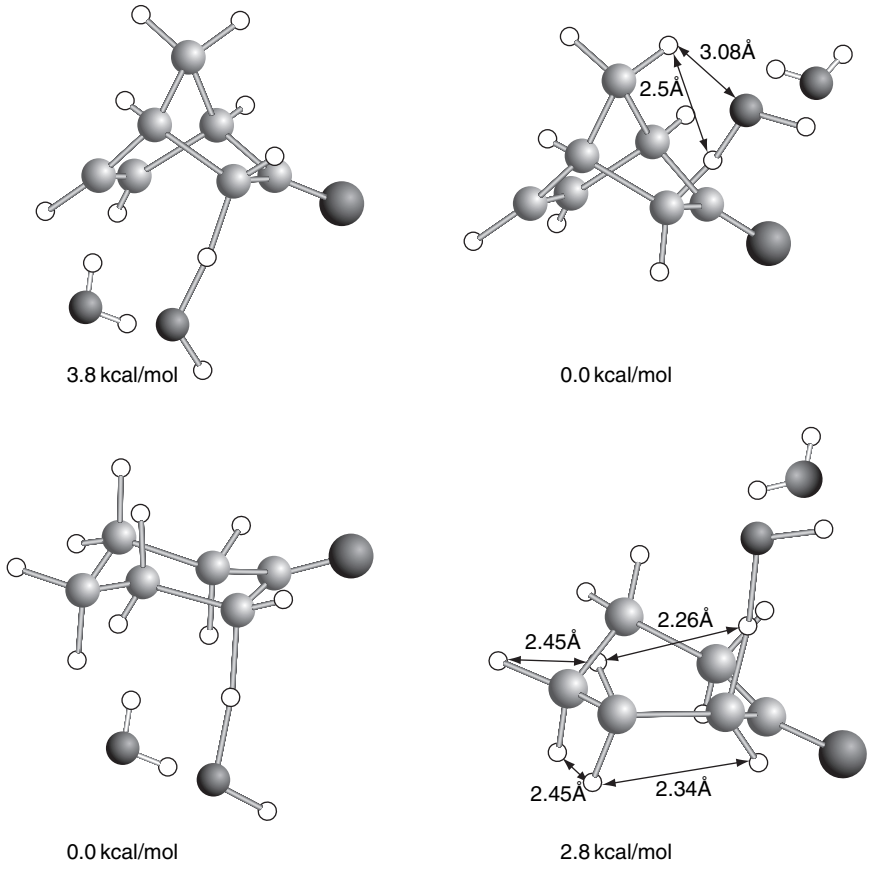


Fig. 6.3. Comparison of transition structures for deprotonation of 2-norbornanone (top) and cyclohexanone (bottom). In 2-norbornanone, *exo* eprotonation is favored by 3.8 kcal/mol. In cyclohexanone, axial deprotonation is favored by 2.8 kcal/mol. Reproduced from *J. Org. Chem.*, **65**, 8970 (2000), by permission of the American Chemical Society.

The cyano group is also effective at stabilizing negative charge on carbon. The minimal steric demands of the cyano group have made it possible to synthesize a number of hydrocarbon derivatives that are very highly substituted with cyano groups. Table 6.9 gives pK values for some of these compounds. As can be seen, the highly substituted derivatives are very strong acids.

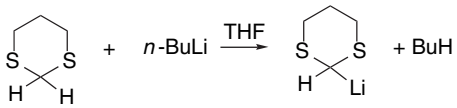
Table 6.9. Acidities of Some Cyanohydrocarbons[a]

Compound	pK
CH_3CN	> 25
$NCCH_2CN$	11.2
$(NC)_3CH$	-5.6
$(NC)_2C{=}C(CN)CH(CN)_2$	< -8.5
Pentacyanocyclopentadiene	< -11.0

a. Selected from data in Tables 5.1 and 5.2 in J. R. Jones, *The Ionization of Carbon Acids*, Academic Press, New York, 1973, pp. 64,65.

Third-row elements, particularly phosphorus and sulfur, stabilize adjacent carbanions. The p*K*'s of some pertinent compounds are given in Table 6.10.

The conjugate base of 1,3-dithiane has proven valuable in synthetic applications as a nucleophile (Part B, Chap.3). The anion is generated by deprotonation using *n*-butyllithium.



The p*K* of 1,3-dithiane is 36.5 (Cs^+ ion pair in THF).[50] The value for 2-phenyl-1,3-dithiane is 30.5. There are several factors that can contribute to the anion-stabilizing effect of sulfur substituents. Bond dipole effects may contribute but cannot be the dominant factor since oxygen does not have a comparable stabilizing influence. Polarizability of sulfur can also stabilize the carbanion. Delocalization can be described as involving 3*d* orbitals on sulfur or hyperconjugation with the σ^* orbital of the C–S bond.[51] An experimental study of the rates of deprotonation of phenylthionitromethane indicates that sulfur polarizability is the major factor.[52] Whatever the structural basis, there is no question that thio substituents enhance the acidity of hydrogens on the adjacent carbons. The phenylthio group increases the acidity of hydrocarbons by at least 15 p*K* units. The effect is from 5–10 p*K* units in carbanions stabilized by other EWGs.[53]

Table 6.10. Acidities of Some Compounds with Sulfur and Phosphorus Substituents

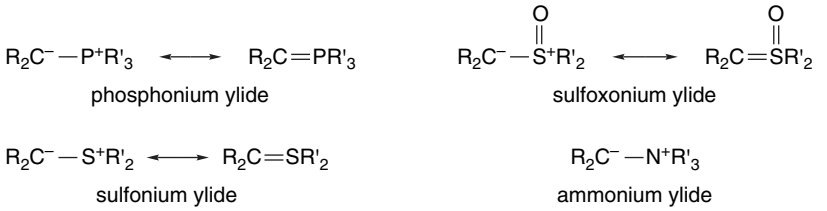
Compound	p*K*(DMSO)
$PhCH_2SPh$[a]	30.8
$PhSO_2CH_3$[b]	29.0
$PhSO_2CH_2Ph$[b]	23.4
$PhCH(SPh)_2$[a]	23.0
$(PhS)_2CH_2$[a]	38.0
$PhSO_2CH_2SPh$[b]	20.3
$PhSO_2CH_2PPh_2$[b]	20.2
$C_2H_5O_2CCH_2PPh_2$[d]	9.2[c]
$PhCOCH_2PPh_2$[d]	6.0[c]

a. F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. E. Drucker, J. Gerhold, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.*, **42,** 326 (1977).
b. F. G. Bordwell, W. S. Matthews, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 442 (1975).
c. In methanol.
d. A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.*, **85**, 2790 (1963).

50. L. Xie, D. A. Bors, and A. Streitwieser, *J. Org. Chem.*, **57**, 4986 (1992).
51. W. T. Borden, E. R. Davidson, N. H. Andersen, A. D. Deniston, and N. D. Epiotis, *J. Am. Chem. Soc.*, **100**, 1604 (1978); A. Streitwieser, Jr., and S. P. Ewing, *J. Am. Chem. Soc.*, **97**, 190 (1975); A. Streitwieser, Jr., and J. E. Williams, Jr., *J. Am. Chem. Soc.*, **97**, 191 (1975); N. D. Epiotis, R. L. Yates, F. Bernardi, and S. Wolfe, *J. Am. Chem. Soc.*, **98**, 5435 (1976); J.-M. Lehn and G. Wipff, *J. Am. Chem. Soc.*, **98**, 7498 (1976); D. A. Bors and A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **108**, 1397 (1986).
52. C. F. Bernasconi and K. W. Kittredge, *J. Org. Chem.*, **63**, 1944 (1998).
53. F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. E. Drucker, J. Gerhold, G. J. McCollum, V. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.*, **42**, 326 (1977); F. G. Bordwell, M. Van Der Puy, and N. R. Vanier, *J. Org. Chem.*, **41**, 1885 (1976).

Trialkyl and triarylsilyl substituents have a modest carbanion-stabilizing effect that is attributed mainly to polarizability and is somewhat greater for the triarylsilyl substituents. This stabilization results in a reduced pK by 1 (trimethylsilyl) to 4 (triphenylsilyl) log units in fluorenes and 3 to 7.5, respectively, in sulfones.[54]

Another important group of nucleophilic carbon species consists of the phosphorus and sulfur ylides. *Ylide* is the name given to molecules in which one of the contributing resonance structures has opposite charges on adjacent atoms when both atoms have octets of electrons. Since we are dealing with nucleophilic carbon species, our interest is in ylides with a negative charge on the carbon. These are of great synthetic importance, and their reactivity is considered in some detail in Chapter 2 of Part B. Here, we discuss the structures of some of the best-known ylides. The three groups of primary synthetic importance are phosphonium, sulfoxonium, and sulfonium ylides. Ylides of ammonium ions also have some synthetic significance.



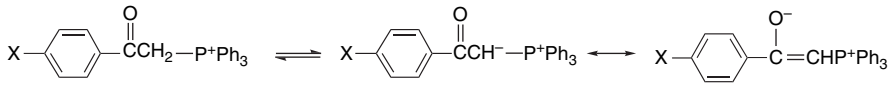
The question of which resonance structure is the principal contributor has been a point of discussion. Since the uncharged *ylene* resonance structures have ten electrons at the phosphorus or sulfur atom, they imply participation of *d* orbitals on the heteroatoms. Such resonance structures are not possible for ammonium ylides. Structural studies indicate that the dipolar ylide structure is the main contributor.[55] The stabilizing effect of phosphonium and sulfonium substituents is primarily the result of dipolar and polarization effects.[56]

The ylides are formed by deprotonation of the corresponding "onium salts."

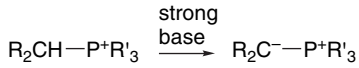
The stability of the ylide is increased by substituent groups that can stabilize the electron-rich carbon.[57] Phosphonium ions with acylmethyl substituents, for example,

54. S. Zhang, X.-M. Zhang, and F. G. Bordwell, *J. Am. Chem. Soc.*, **117**, 602 (1995); A. Streitwieser, L. Xie, P. Wang, and S. M. Bachrach, *J. Org. Chem.*, **58**, 1778 (1993).
55. H. Schmidbaur, W. Buchner, and D. Scheutzow, *Chem. Ber.*, **106**, 1251 (1973); D. G. Gilheany, in *The Chemistry of Organophosphorus Compounds*, F. R. Hartley, ed., Wiley, New York, 1994, pp. 1–44; S. M. Bachrach and C. I. Nitsche, in *The Chemistry of Organophosphorus Compounds*, F. R. Hartley, ed., Wiley, New York, 1994, pp. 273–302.
56. X.-M. Zhang and F. G. Bordwell, *J. Am. Chem. Soc.*, **116**, 968 (1994).
57. M. Schlosser, T. Jenny, and B. Schaub, *Heteroatom. Chem.*, **1**, 151 (1990).

are quite acidic. A series of aroylmethyl phosphonium ions has pK values of 4–7, with the precise value depending on the aryl substituents.[58]



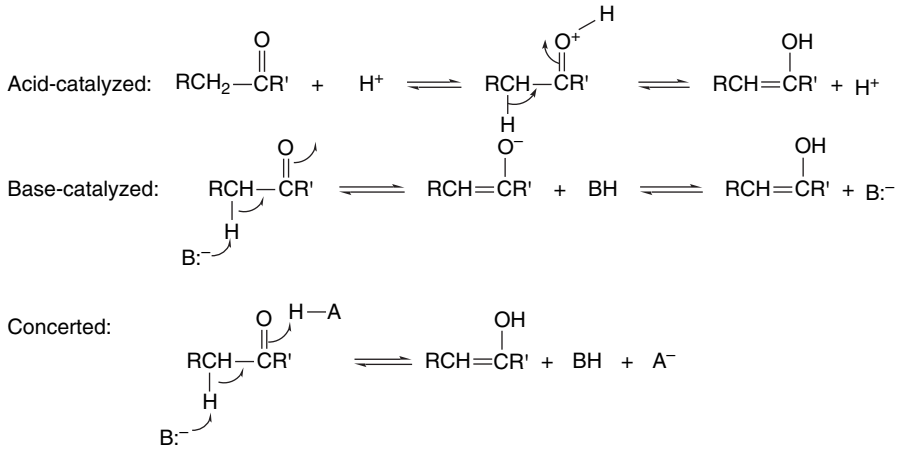
In the absence of the carbonyl or similar stabilizing group, the onium salts are less acidic. The pK_{DMSO} of methyltriphenylphosphonium ion is estimated to be 22. Strong bases such as amide ion or the anion of DMSO are required to deprotonate alkylphosphonium salts.



Similar considerations apply to the sulfoxonium and sulfonium ylides, which are formed by deprotonation of the corresponding positively charged sulfur-containing cations. The additional electronegative oxygen atom in the sulfoxonium salts stabilizes these ylides considerably, relative to the sulfonium ylides.[59]

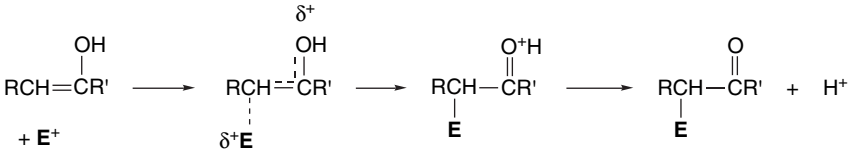
6.4. Enols and Enamines

Carbonyl compounds can act as carbon nucleophiles in the presence of *acid catalysts*, as well as bases. The nucleophilic reactivity of carbonyl compounds in acidic solution is due to the presence of the *enol tautomer*. The equilibrium between carbonyl compounds and the corresponding enol can be acid- or base-catalyzed and can also occur by a concerted mechanism in which there is concurrent protonation and deprotonation. As we will see shortly, the equilibrium constant is quite small for monocarbonyl compounds, but the presence of the enol form permits reactions that do not occur from the carbonyl form.

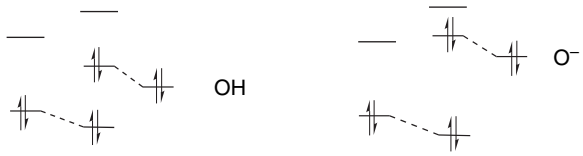


[58] S. Fliszar, R. F. Hudson, and G. Salvadori, *Helv. Chim. Acta*, **46**, 1580 (1963).
[59] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

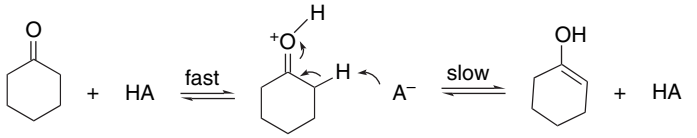
Like simple alkenes, enols are nucleophilic by virtue of their π electrons. Enols are much more reactive than simple alkenes, however, because the hydroxy group participates as an electron donor during the reaction process. The oxygen is deprotonated and the strong C=O bond is formed, providing a favorable energy contribution.



Enols are not as reactive as enolate anions, however. This lower reactivity reflects the presence of the additional proton in the enol, which decreases the electron density of the enol relative to the enolate. In MO terminology, the −OH and $-O^-$ donor substituents both raise the energy of the π-HOMO, but the O^- group is the better donor.



A number of studies of the acid-catalyzed mechanism of enolization have been done, and the case of cyclohexanone is illustrative.[60] The reaction is catalyzed by various carboxylic acids and substituted ammonium ions. The effectiveness of these proton donors as catalysts correlates with their pK_a values. When plotted according to the Brønsted catalysis law (Section 3.6.1) the value of the slope α is 0.74. When deuterium or tritium is introduced in the α-position, there is a marked decrease in the rate of acid-catalyzed enolization: $k_H/k_D \sim 5$. This kinetic isotope effect indicates that the C–H bond cleavage is part of the rate-determining step. The generally accepted mechanism for acid-catalyzed enolization pictures the rate-determining step as deprotonation of the protonated ketone.

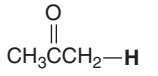
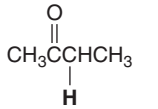
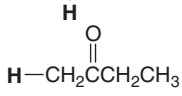
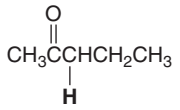
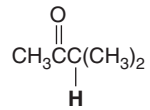
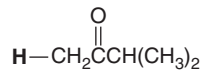
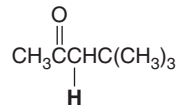
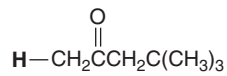


It is possible to measure the rate of enolization by isotopic exchange. NMR spectroscopy provides a very convenient method for following hydrogen-deuterium exchange. Data for several ketones are given in Table 6.11.

A point of contrast with the data for base-catalyzed removal of a proton (see Table 6.8) is the tendency for acid-catalyzed enolization to result in preferential formation of the *more-substituted enol*. For 2-butanone, the ratio of exchange at CH_2 to that at CH_3 is 4.2:1, after making the statistical correction for the number of hydrogens. The preference for acid-catalyzed enolization to give the more-substituted enol is the result of the stabilizing effect that alkyl groups have on carbon-carbon double bonds. To the extent that the TS resembles product,[61] alkyl groups stabilize the

60. G. E. Lienhard and T.-C. Wang, *J. Am. Chem. Soc.*, **91**, 1146 (1969).
61. C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **80**, 5885 (1958).

Table 6.11. Relative Rates of Acid-Catalyzed Enolization of some Ketones[a]

Ketone	Relative rate
	100
	220
	76
	171
	195
	80
	46
	105

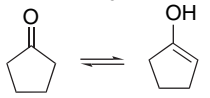
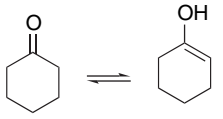
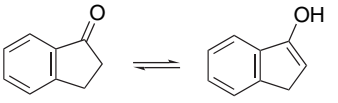
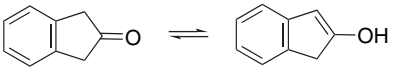
a. In D_2O-dioxane with DCl catalyst. The data of C. Rappe and W. H. Sachs, *J. Org. Chem.*, **32**, 3700 (1967), given on a per group basis have been converted to a per-hydrogen basis.

more branched TS. There is an opposing steric effect that appears to be significant for 4,4-dimethyl-2-pentanone, in which the methylene group that is flanked by a *t*-butyl group is less reactive than the methyl group. The overall range of reactivity differences in acid-catalyzed exchange is much less than for base-catalyzed exchange, however (compare Tables 6.8 and 6.11). This is consistent with the C-deprotonation of the O-protonated compound having an earlier TS.

There are extensive data on the equilibrium constant for enolization. Table 6.12 gives data on the amount of enol present at equilibrium for some representative compounds. For simple aldehydes, the K_{enol} is the range 10^{-4} to 10^{-5}. Ketones have *smaller* enol content, with K_{enol} around 10^{-8}. For esters and amides, where the carbonyl form is resonance stabilized, the K_{enol} drops to 10^{-20}. Somewhat surprisingly, 1-aryl substituents do not have a large effect on enol content, as in acetophenone, probably because there is conjugation in the ketone as well as in the enol. On the other hand, there is a large difference when the aryl group is β to the carbonyl, as in 2-indanone, which has a much higher enol content than 1-indanone.

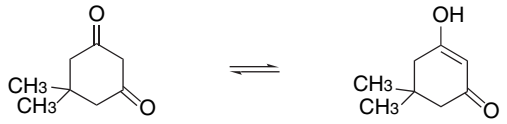
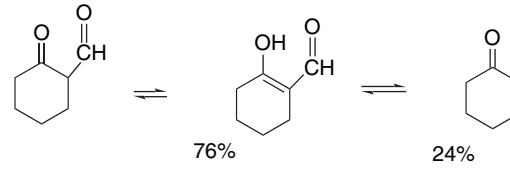
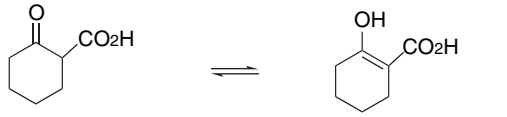
The amount of enol present at equilibrium is influenced by other substituent groups. In the case of compounds containing a single ketone, aldehyde, or ester

Table 6.12. Equilibrium Constants for Enolization of Some Carbonyl Compounds

	Enolization equilibrium	*K* enol/keto
1[b]	$CH_3CH{=}O \rightleftharpoons CH_2{=}CHOH$	10^{-5}
2[c]	$(CH_3)_2CHCH{=}O \rightleftharpoons (CH_3)_2C{=}CHOH$	1.4×10^{-4}
3[d]	$PhCH_2CH{=}O \rightleftharpoons PhCH{=}CHOH$	8.5×10^{-4}
4[e]	$CH_3\overset{\overset{O}{\|}}{C}CH_3 \rightleftharpoons CH_2{=}\overset{\overset{OH}{\|}}{C}CH_3$	1.3×10^{-8}
5[e]	$CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2CH_3 \rightleftharpoons CH_3CH{=}\overset{\overset{OH}{\|}}{C}CH_2CH_3$	3.7×10^{-8}
6[e]	$(CH_3)_2CH\overset{\overset{O}{\|}}{C}CH(CH_3)_2 \rightleftharpoons (CH_3)_2C{=}\overset{\overset{OH}{\|}}{C}CH(CH_3)_2$	3.0×10^{-8}
7[e]	$PhC(=O)CH_3 \rightleftharpoons PhC(OH){=}CH_2$	1.1×10^{-8}
8[e]	$PhC(=O)CH(CH_3)_2 \rightleftharpoons PhC(OH){=}C(CH_3)_2$	3.3×10^{-7}
9[e]		1.2×10^{-8}
10[e]		4.2×10^{-7}
11[f]	$CH_3C(=O)OCH_3 \rightleftharpoons CH_2{=}C(OH)OCH_3$	3.2×10^{-19}
12[f]	$CH_3C(=O)NH_2 \rightleftharpoons CH_2{=}C(OH)NH_2$	6.3×0^{-20}
13[g]		3.3×10^{-8}
14[h]		1.5×10^{-4}
15[i]	$CH_3C(=O)CH_2C(=O)CH_3 \rightleftharpoons CH_3C(OH){=}CHC(=O)CH_3$	2.3×10^{-1} (H_2O)
16[j]		29 (CCl_4)
17[i]	$CH_3C(=O)CH_2C(=O)OC_2H_5 \rightleftharpoons CH_3C(OH){=}CHC(=O)OC_2H_5$	7×10^{-2} (H_2O)
18[j]		3×10^{-1} (CCl_4)
19[i]	$CH_3C(=O)CH_2C(=O)NH_2 \rightleftharpoons CH_3C(OH){=}CHC(=O)NH_2$	1.3 (H_2O)

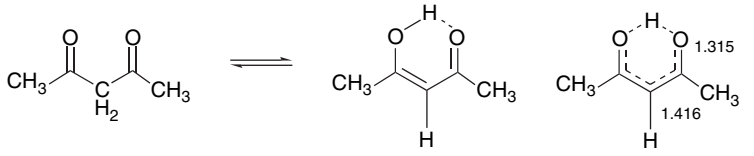
(*Continued*)

Table 6.12. (*Continued*)

Enolization equilibrium	*K* enol/keto
20[j] 	20 (H_2O) 0.05 ($CHCl_3$)
21[k]  76% 24%	> 50(CCl_4)
22[l] 	5.4×10^{-2} (H_2O)

a. In water unless otherwise noted.
b. J. P. Guthrie and P. A. Cullimore, *Can. J. Chem.*, **57**, 240 (1979).
c. Y. Chiang, A. J. Kresge, and P. A. Walsh, *J. Am. Chem. Soc.*, **108**, 6314 (1986).
d. Y. Chiang, A. J. Kresge, P. A. Walsh, and Y. Yin, *J. Chem. Soc., Chem. Commun.*, 869 (1989).
e. J. R. Keefe, A. J. Kresge, and N. P. Schepp, *J. Am. Chem. Soc.*, **112**, 4862 (1990).
f. J. P. Richard, G. Williams, A. M. C. O'Donoghue, and T. L. Amyes, *J. Am. Chem. Soc.*, **124**, 2957 (2002).
g. E. A. Jefferson, J. R. Keefe, and A. J. Kresge, *J. Chem. Soc. Perkin Trans. 2*, 2041 (1995).
h. J. R. Keefe, A. J. Kresge, and Y. Yin, *J. Am. Chem. Soc.*, **110**, 8201 (1988).
i. J. W. Bunting and J. P. Kanter, *J. Am. Chem. Soc.*, **115**, 11705 (1993).
j. S. G. Mills and P. Beak, *J. Org. Chem.*, **50**, 1216 (1985).
k. E. W. Garbisch, *J. Am. Chem. Soc.*, **85**, 1696 (1963).
l. J. A. Chang, A. J. Kresge, V. A. Nikolaev, and V. V. Popik, *J. Am. Chem. Soc.*, **125**, 6478 (2003).

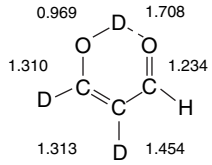
function, very little of the enol is present at equilibrium. When two such groups are close to one another, particularly if they are separated by a single carbon atom, the enol may be the major form. The enol forms of ß-diketones and ß-ketoesters are stabilized by intramolecular hydrogen bonds and by conjugation of the carbon-carbon double bond with the carbonyl group. The structural data given below for the enol form of 2,4-pentanedione were obtained by an electron diffraction study.[62] In this case the data pertain to the time-averaged structure resulting from proton transfer between the two hydrogen-bonded oxygens.



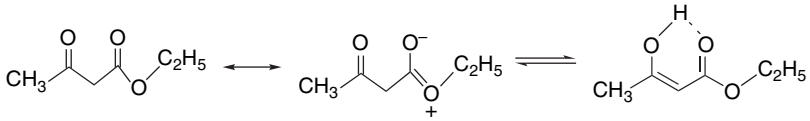
The simplest compound with this type of enolic structure is malonaldehyde. The structures determined by microwave spectroscopy on a deuterated analog have provided

62. A. H. Lowrey, C. George, P. D'Antonio, and J. Karle, *J. Am. Chem. Soc.*, **93,** 6399 (1971).

the bond length data shown below.[63] The barrier for shift of the enolic hydrogen (or deuterium) between the two oxygen atoms is about 4–5 kcal.[64]

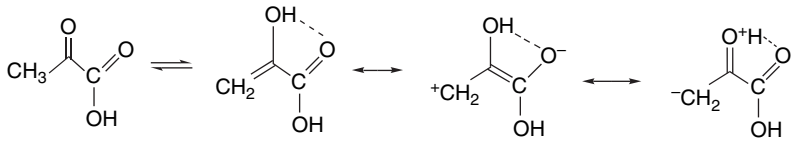


The extent of enolization at equilibrium is also solvent dependent.[65] The hydrogen-bonding capacity of the solvent is especially important. For example, for ethyl acetoacetate, the amount of enol is higher (15–30%) in nonpolar solvents such as carbon tetrachloride or benzene than in more polar solvents such as water or acetone (5% enol in acetone, 1% enol in water).[66] The strong intramolecular hydrogen bond in the enol form minimizes the molecular dipole by reducing the negative charge on the oxygen of the carbonyl group. In more polar solvents this stabilization is less important, and in protic solvents such as water, hydrogen bonding by the solvent is dominant.



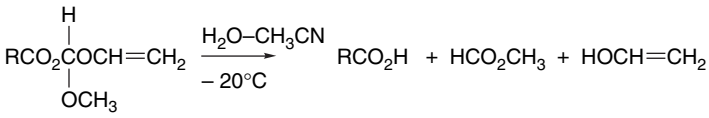
This relationship is reversed in compounds where intramolecular hydrogen bonding is not possible. (See the entry for 5,5-dimethylcyclohexane-1,3-dione in Table 6.12.)

α-Dicarbonyl compounds also have an enhanced tendency toward enolization, although it is not as pronounced as for β-dicarbonyl compounds. The K_{enol} for pyruvic acid is about 10^{-3}.[67] There is resonance stabilization between the enol double bond and the ester carbonyl as well as a contribution from hydrogen bonding.



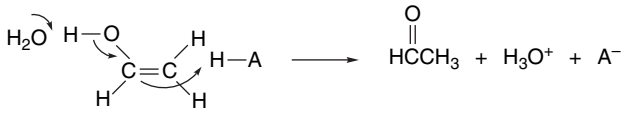
Enols of simple ketones can be generated in high concentrations as metastable species by special techniques.[68] Vinyl alcohol, the enol of acetaldehyde, can be generated by very careful hydrolysis of any of several ortho ester derivatives in which the group RCO_2^- is acetic acid or a chloroacetic acid.[69]

63. S. L. Baughcum, R. W. Duerst, W. F. Rowe, Z. Smith, and E. B. Wilson, *J. Am. Chem. Soc.*, **103**, 6296 (1981).
64. S. L. Baughcum, Z. Smith, E. B. Wilson, and R. W. Duerst, *J. Am. Chem. Soc.*, **106**, 2260 (1984).
65. J. Elmsley and N. J. Freeman, *J. Mol. Struct.*, **161**, 193 (1987); J. N. Spencer, E. S. Holcombe, M. R. Kirshenbaum, D. W. Firth, and P. B. Pinto, *Can. J. Chem.*, **60**, 1178 (1982).
66. K. D. Grande and S. M. Rosenfeld, *J. Org. Chem.*, **45,** 1626 (1980); S. G. Mills and P. Beak, *J. Org. Chem.*, **50**, 1216 (1985).
67. Y. Chiang, A. J. Kresge, and P. Pruszynski, *J. Am. Chem. Soc.*, **114,** 3103 (1992); J. Damitio, G. Smith, J. E. Meany, and Y. Pocker, *J. Am. Chem. Soc.*, **114**, 3081 (1992).
68. B. Capon, B. Z. Guo, F. C. Kwok, A. F. Siddhanta, and C. Zucco, *Acc. Chem. Res.*, **21**, 135 (1988).
69. B. Capon, D. S. Rycroft, T. W. Watson, and C. Zucco, *J. Am. Chem. Soc.*, **103**, 1761 (1981).

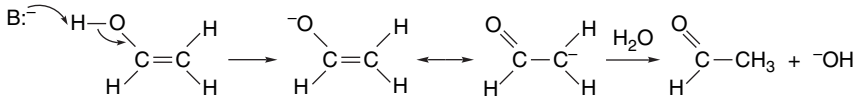


The enol can be observed by NMR and at −20°C has a half-life of several hours. At +20°C the half-life is only 10 min. The presence of bases causes very rapid isomerization to acetaldehyde via the enolate. Solvents have a significant effect on the lifetime of such unstable enols. Solvents such as DMF or DMSO, which are known to slow the rate of proton exchange by hydrogen bonding, increase the lifetime of unstable enols.[70]

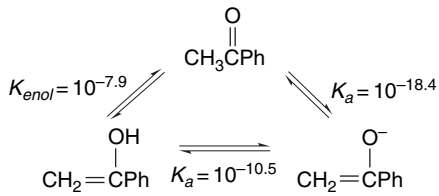
Solutions of unstable enols of simple ketones and aldehydes can also be generated in water by the addition of a solution of the enolate.[71] The initial protonation takes place on oxygen, generating the enol, which is then ketonized at a rate that depends on the solution pH. The ketonization exhibits both acid and base catalysis.[72] Acid catalysis involves C-protonation with concerted O-deprotonation. In agreement with expectation for a rate-determining proton transfer, the reaction shows general acid catalysis.



Base-catalyzed ketonization occurs by C-protonation of the enolate.

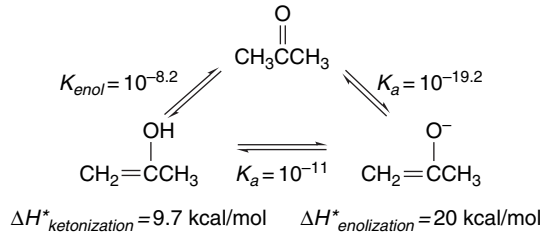


As would be expected on the basis of electronegativity arguments, enols are much more acidic than the corresponding keto form. It has been possible to determine the pK of the enol form of acetophenone as being 10.5 in water. The pK of the keto form is 18.4.[73] Since the enolate is the same for both equilibria, the difference in the pK values is equal to the enol ⇌ keto equilibrium constant, K_{enol}.



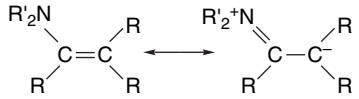
Similar measurements have been made for the equilibria involving acetone and its enol, 2-hydroxypropene.[74] In this case, the activation parameters were also determined and are shown below.[75]

70. E. A. Schmidt and H. M. R. Hoffmann, *J. Am. Chem. Soc.*, **94**, 7832 (1972).
71. Y. Chiang, A. J. Kresge, and P. A. Walsh, *J. Am. Chem. Soc.*, **104**, 6122 (1982); Y. Chiang, A. J. Kresge, and P. A. Walsh, *J. Am. Chem. Soc.*, **108**, 6314 (1986).
72. B. Capon and C. Zucco, *J. Am. Chem. Soc.*, **104**, 7567 (1982).
73. Y. Chiang, A. J. Kresge, and J. Wirz, *J. Am. Chem. Soc.*, **106**, 6392 (1984).
74. Y. Chiang, A. J. Kresge, Y. S. Tang, and J. Wirz, *J. Am. Chem. Soc.*, **106**, 460 (1984).
75. Y. Chiang, A. J. Kresge, and N. P. Schepp, *J. Am. Chem. Soc.*, **111**, 3977 (1989).

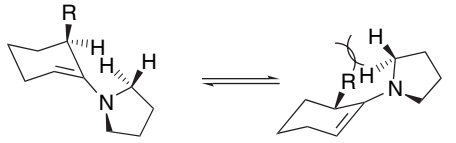


The accessibility of enols and enolates, respectively, in acidic and basic solutions of carbonyl compounds makes possible a wide range of reactions that depend on their nucleophilicity. These reactions are discussed in Chapter 7 and in Chapters 1 and 2 of Part B.

Amino substituents on a carbon-carbon double bond enhance the nucleophilicity of the ß-carbon to an even greater extent than the hydroxy group in enols because of the greater electron-donating power of nitrogen. Such compounds are called *enamines*.[76]



An interesting and useful property of enamines of 2-alkylcyclohexanone is the substantial preference for the less-substituted isomer to be formed. This tendency is especially pronounced for enamines derived from cyclic secondary amines such as pyrrolidine, a preference that can be traced to $A^{1,3}$ allylic strain. In order to maximize conjugation between the nitrogen lone pair and the carbon-carbon double bond, the nitrogen substituent must be coplanar with the double bond. This creates a steric repulsion when the enamine bears a ß-substituent and leads to a preference for the unsubstituted enamine. Because of the same preference for coplanarity in the enamine system, α-alkyl substituents adopt an axial conformation to minimize steric interaction with the amino group.



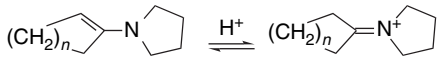
favored conformation

These steric factors are also indicated by the relative basicity of enamines derived from five- , six- , and seven-membered ketones.[77] The five- and seven-membered enamines

[76] A. G. Cook, *Enamines*, 2nd Edition, Marcel Dekker, New York, 1988, Chap. 1; Z. Rappoport, ed., *Chemistry of Enamines*, Wiley, Chichester, 1994.

[77] A. G. Cook, M. L. Absi, and V. F. Bowden, *J. Org. Chem.*, **60**, 3169 (1995).

are considerably stronger bases, indicating better conjugation between the nitrogen lone pair and the double bond. The reduced basicity of the cyclohexanone enamines is related to the preference for *exo* and *endo* double bonds in six-membered rings.



n	pK_a
2	2.7
3	4.5
4	1.7

The preparation of enamines is discussed in Chapter 7, and their application as carbon nucleophiles in synthesis is dealt with in Chapter 1 of Part B.

6.5. Carbanions as Nucleophiles in S_N2 Reactions

Carbanions are very useful intermediates in the formation of carbon-carbon bonds. This is true for both unstabilized structures found in organometallic reagents and stabilized structures such as enolates. Carbanions can participate as nucleophiles in both addition and substitution reactions. At this point we consider aspects of the reactions of carbanions as nucleophiles in reactions that proceed by the S_N2 mechanism. Other synthetic applications of carbanions are discussed more completely in Chapter 7 and in Chapters 1 and 2, Part B.

6.5.1. Substitution Reactions of Organometallic Reagents

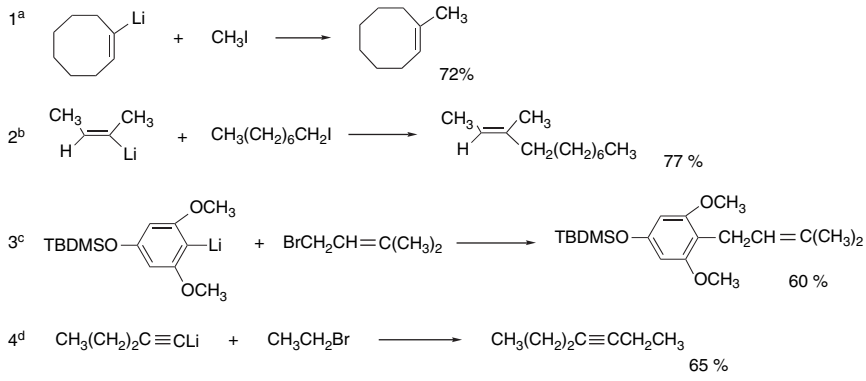
Carbanions are classified as soft nucleophiles. They are expected to be good nucleophiles in S_N2 reactions and this is generally true. The reactions of aryl-, alkenyl- , and allyl lithium reagents with primary alkyl halides and tosylates appear to proceed by S_N2 mechanisms. Similar reactions occur between arylmagnesium halides (Grignard reagents) and alkyl sulfates and sulfonates. Some examples of these reactions are given in Scheme 6.2.

Note that all the examples in Scheme 6.2 involve either sp^2 or stabilized organometallic reagents. Evidence for an S_N2-type mechanism in the reaction of allyl and benzyl lithium reagents has been obtained from stereochemical studies. With 2-bromobutane, both of these reagents react with complete inversion of configuration.[78] *n*-Butyllithium, however, gives largely racemic product, indicating that some competing process must also be occurring.[79] A general description of the mechanism for the reaction of organolithium compounds with alkyl halides must take account of the structure of the organometallic compound. It is known that halide anions are accommodated into typical organolithium cluster structures and can replace solvent molecules as ligands. A similar process in which the alkyl halide became complexed

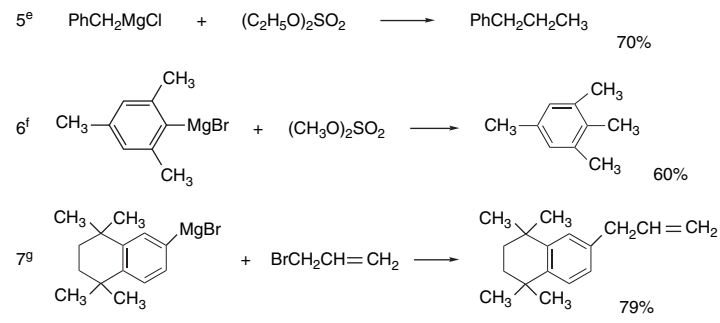
[78] L. H. Sommer and W. D. Korte, *J. Org. Chem.*, **35**, 22 (1970).
[79] H. D. Zook and R. N. Goldey, *J. Am. Chem. Soc.*, **75**, 3975 (1953).

Scheme 6.2. Alkylation Reactions of Some Organometallic Reagents

A. Organolithium Reagents

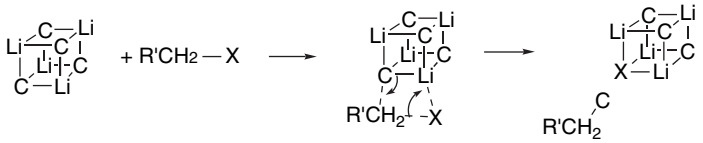


B. Organomagnesium reagents

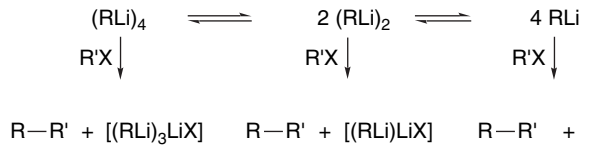


a. H. Neumann and D. Seebach, *Chem. Ber.*, **111**, 2785 (1978).
b. J. Millon, R. Lorne, and G. Linstrumelle, *Synthesis*, 434 (1975).
c. T. L. Shih, M. J. Wyvratt, and H. Mrozik, *J. Org. Chem.*, **52**, 2029 (1987).
d. A. J. Quillinan and F. Schienman, *Org. Synth.*, **58**, 1 (1978).
e. H. Gilman and W. E. Catlin, *Org. Synth.*, **I**, 360 (1943).
f. L. I. Smith, *Org. Synth.*, **II**, 360 (1943).
g. J. Eustache, J. M. Bernardon, and B. Shroot, *Tetrahedron Lett.*, **28**, 4681 (1987).

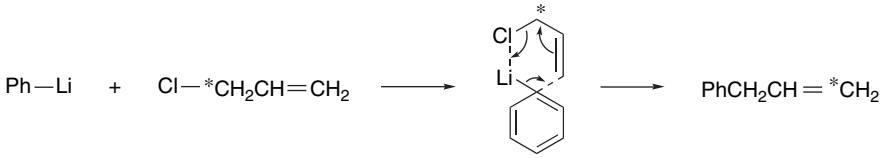
at lithium would provide an intermediate structure that could account for the subsequent alkylation. This process is represented below for a tetrameric structure, with the organic group simply represented by C.



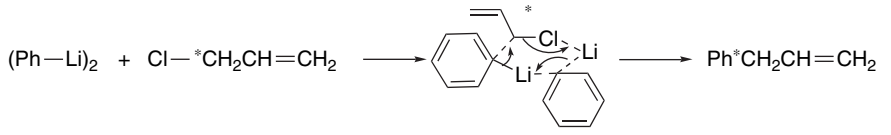
In general terms, the reactions of organolithium reagents with alkylating agents might occur at any of the aggregation stages present in solution and there could be reactivity differences among them. There has been little detailed mechanistic study that would distinguish among these possibilities.



The reaction of phenyllithium and allyl chloride using ^{14}C label reveals the occurrence of allylic transposition. About three-fourths of the product results from bond formation at C(3) rather than C(1), which can be accounted for by a cyclic mechanism.[80]



The portion of the product formed by reaction at C(1) in allylic systems may form by direct substitution, but it has also been suggested that a cyclic TS involving an aryllithium dimer might be involved.



These mechanisms ascribe importance to the Lewis acid–Lewis base interaction between the allyl halide and the organolithium reagent. When substitution is complete, the halide ion is incorporated into the lithium cluster in place of one of the carbon ligands.

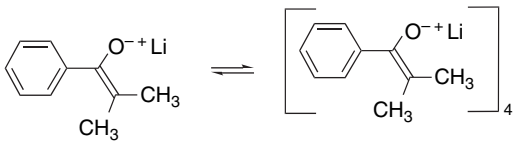
From a synthetic point of view, direct alkylation of lithium and magnesium organometallic compounds has been largely supplanted by transition metal–catalyzed processes. We discuss these reactions in Chapter 8 of Part B.

6.5.2. Substitution Reactions of Enolates

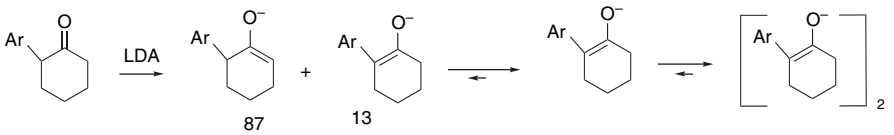
The alkylation reactions of enolate anions of both ketones and esters have been extensively utilized in synthesis. Both stable enolates, such as those derived from ß-ketoesters, ß-diketones, and malonate esters, as well as less stable enolates of monofunctional ketones, esters, nitriles, etc., are reactive. Many aspects of the relationships among reactivity, stereochemistry, and mechanism have been clarified. The starting point for the discussion of these reactions is the structure of the enolates. Studies of ketone enolates in solution indicate that both tetrameric and dimeric clusters can exist. THF, a solvent in which many synthetic reactions are performed, favors tetrameric structures for the lithium enolate of isobutyrophenone, for example.[81]

[80] R. M. Magid and J. G. Welch, *J. Am. Chem. Soc.*, **90**, 5211 (1968); R. M. Magid, E. C. Nieh, and R. D. Gandour, *J. Org. Chem.*, **36**, 2099 (1971).

[81] L. M. Jackman and N. Szeverenyi, *J. Am. Chem. Soc.*, **99**, 4954 (1977); L. M. Jackman and B. C. Lange, *Tetrahedron*, **33**, 2737 (1977).



Detailed investigation of the degree of aggregation in solution has been applied to several alkyl aryl ketones.[82] The lithium enolate of 4-(4-biphenyl)-2-methyl-1-propanone in THF exhibits a monomer-tetramer equilibrium.[83] The K_{eq} for tetramerization is estimated as $5 \times 10^8 M^3$, which corresponds to 1.3% of the enolate being present as the monomer. The kinetics of the alkylation reaction with benzyl bromide indicates that the *monomer is the reactive nucleophile*. Related studies were carried out with 2-(4-biphenyl)cyclohexanone. In this case, an initial 87:13 mixture of the regioisomeric enolates is completely converted to the conjugated enolate at equilibrium. There is an equilibrium between monomer and dimer, with $K_{eq} = 4.3 \times 10^3\, M$. Again, the monomer is more reactive in the alkylation reaction. This is attributed to less electrostatic stabilization by a single Li^+ than by two or four in the aggregates.



The structures of several lithium enolates of ketones have been determined by X-ray crystallography and reveal aggregated structures in which oxygen and lithium occupy alternating corners of distorted cubes. Figure 6.4 illustrates some of the observed structures. Figure 6.4a shows an unsolvated enolate of methyl *t*-butyl ketone (pinacolone).[84] The structures in Figures 6.4b and 6.4c are THF solvates of the enolates of methyl *t*-butyl ketone and cyclopentanone, respectively.[85] Each of these structures consists of clusters of four enolate anions and four lithium cations arranged with lithium and oxygen at alternating corners of a distorted cube. The structure in Figure 6.4d includes only two enolate anions. Four lithium ions are present, along with two di-*i*-propylamide ion. A significant feature of this structure is the coordination of the remote silyloxy oxygen atom to one of the lithium cations.[86] This is an example of the Lewis acid–Lewis base interactions that are frequently involved in organizing TS structure in the reactions of lithium enolates. A common feature of all four of the structures is the involvement of the enolate oxygen in multiple contacts with lithium cations in the cluster. An approaching electrophile will clearly be somewhat hindered from direct contact with oxygen in such structures, whereas the nucleophilic carbon is somewhat more exposed.

82. A.Streitwieser and D. Z.-R. Wang, *J. Am. Chem. Soc.*, **121**, 6213 (1999).
83. A. Abbotto, S. S.-W. Leung, A. Streitwieser, and K. V. Kilway, *J. Am. Chem. Soc.*, **120**, 10807 (1998).
84. P. G. Williard and G. B. Carpenter, *J. Am. Chem. Soc.*, **107**, 3345 (1985).
85. R. Amstutz, W. B. Schweizer, D. Seebach, and J. D. Dunitz, *Helv. Chim. Acta*, **64**, 2617 (1981).
86. P. G. Williard and M. J. Hintze, *J. Am. Chem. Soc.*, **109**, 5539 (1987).

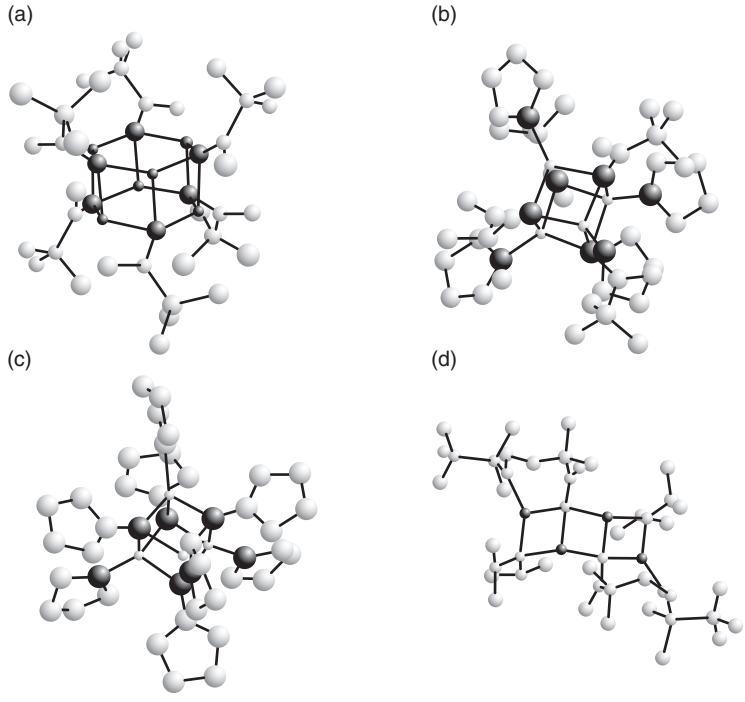


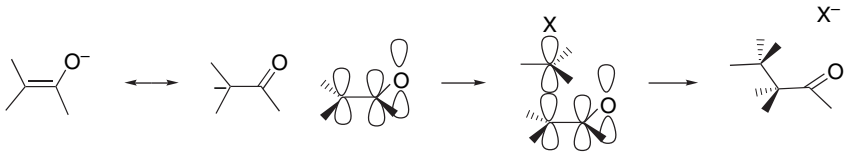
Fig. 6.4. Crystal structures of some enolates of ketones: (a) unsolvated hexameric enolate of methyl *t*-butyl ketone; (b) THF solvate of tetrameric enolate of methyl t-butyl ketone; (c) THF solvate of tetrameric enolate of cyclopentanone; and (d) dimeric enolate of 3,3-dimethyl-4-(*t*-butyldimethylsilyloxy-2-pentanone. Adapted from *J. Am. Chem. Soc.*, **107**, 3345 (1985); *Helv. Chim. Acta*, **64**, 2617 (1981); *J. Am. Chem. Soc.*, **107**, 5403 (1985); and *J. Am. Chem. Soc.*, **109**, 5539 (1987), by permission of the American Chemical Society and Wiley-VCH.

Several ester enolates have also been examined by X-ray crystallography.[87] The enolates of *t*-butyl propionate and *t*-butyl 3-methylpropionate were obtained as TMEDA solvates of enolate dimers. Methyl 3,3-dimethylbutanoate was obtained as a THF-solvated tetramer.

Most of the structural features of enolates are correctly modeled using B3LYP/6-31+G* computations with dimethyl ether as the solvent molecule.[88] Computational methods also indicate the stability of aggregated structures. Both ab initio and semiempirical calculations of the structure of the lithium enolate of methyl isobutyrate have been reported.[89] Although semiempirical PM3 calculations give adequate representations of the geometries of the aggregates, the energy values are not accurate. Dimeric and tetrameric structures give calculated ^{13}C chemical shifts in agreement with the experimental values.

87. D. Seebach, R. Amstutz, T. Laube, W. B. Schweizer, and J. D. Dunitz, *J. Am. Chem. Soc.*, **107**, 5403 (1985).
88. A. Abbotto, A. Streitwieser, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **119**, 11255 (1997).
89. H. Weiss, A. V. Yakimansky, and A. H. E. Mueller, *J. Am. Chem. Soc.*, **118**, 8897 (1996).

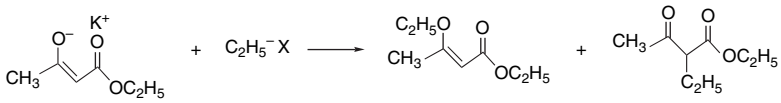
Because of the delocalized nature of enolates, an electrophile can attack either at oxygen or at carbon. Soft electrophiles prefer carbon and it is found experimentally that most alkyl halides react to give C-alkylation. Because of the π character of the HOMO of the anion, there is a stereoelectronic preference for attack of the electrophile approximately perpendicular to the plane of the enolate. The frontier orbital is ψ_2 with electron density mainly at O and C(2). The TS for an S_N2 alkylation of an enolate can be represented as below.



One of the general features of the reactivity of enolate anions is the sensitivity of both the reaction rate and the ratio of C versus O alkylation to the degree of aggregation of the enolate. For example, addition of HMPA frequently increases the rate of enolate alkylation reactions.[90] Use of a dipolar aprotic solvent such as DMF or DMSO in place of THF also leads to rate acceleration.[91] These effects are attributed, at least in part, to dissociation of the enolate aggregates. Similar effects are observed when crown ethers or other cation-complexing agents are added to reaction mixtures.[92] The order of enolate reactivity also depends on the metal cation that is present. The general order is BrMg < Li < Na < K, which is also in the order of greater dissociation of the enolate-cation ion pairs and ion aggregates. Carbon-13 chemical shift data provide an indication of electron density at the nucleophilic carbon in enolates. These shifts have been found to be both cation and solvent dependent. Apparent electron density is in the order $K^+ > Na^+ > Li^+$ and THF/HMPA > DME > THF > ether.[93] There is a good correlation with observed reactivity under the corresponding conditions.

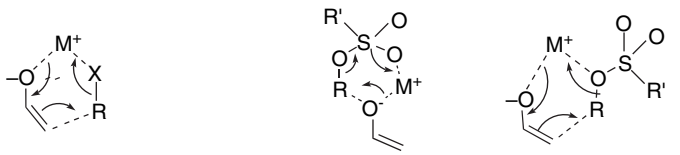
The leaving group in the alkylating reagent has a major effect on whether C- or O-alkylation occurs. The C- versus O-alkylation ratio has been studied for the potassium salt of ethyl acetoacetate as a function of both solvent and leaving group.[94]

90. L. M. Jackman and B. C. Lange, *J. Am. Chem. Soc.*, **103**, 4494 (1981); C. L. Liotta and T. C. Caruso, *Tetrahedron Lett.*, **26**, 1599 (1985).
91. H. D. Zook and J. A. Miller, *J. Org. Chem.*, **36**, 1112 (1971); H. E. Zaugg, J. F. Ratajczyk, J. E. Leonard, and A. D. Schaeffer, *J. Org. Chem.*, **37**, 2249 (1972); H. E. Zaugg, *J. Am. Chem. Soc.*, **83**, 837 (1961).
92. A. L. Kurts, S. M. Sakembaeva, J. P. Beletskaya, and O. A. Reutov, *Zh. Org. Khim. SSSR*, (Engl. Transl.), **10**, 1588 (1974).
93. H. O. House, A. V. Prabhu, and W. V. Phillips, *J. Org. Chem.*, **41**, 1209 (1976).
94. A. L. Kurts, A. Macias, N. K. Genkina, I. P. Beletskaya, and O. A. Reutov, *Dokl. Akad. Nauk, SSSR* (Engl. Trans.), **187**, 595 (1969); A. L. Kurts, N. K. Genkina, A. Macias, I. P. Beletskaya, and O. A. Reutov, *Tetrahedron*, **27**, 4777 (1971).



Leaving group X	Solvent	C:O ratio	Leaving group X	Solvent	C:O ratio
$OSO_2OC_2H_5$	THF	100:0	$OSO_2C_7H_7$	HMPA	12:88
$OSO_2OC_2H_5$	*t*-BuOH	100:0	Cl	HMPA	40:60
$OSO_2OC_2H_5$	EtOH	92:8	Br	HMPA	61:39
$OSO_2OC_2H_5$	CH_3CN	68:32	I	HMPA	87:13
$OSO_2OC_2H_5$	DMSO	30:70			
$OSO_2OC_2H_5$	DMF	21:79			
$OSO_2OC_2H_5$	HMPA	17:83			

These data show that a change from a hard leaving group (sulfonate, sulfate) to a softer leaving group (bromide, iodide) favors carbon alkylation. Another possible factor in C:O ratios may be the ability of sulfonates to form a six-membered cyclic TS for both modes of reaction, whereas halides can form such structures only for C-alkylation.[83]



6-membered TS available only for C-alkylation

6-membered TS available for both C-and O-alkylation

The data for ethyl acetoacetate alkylation also show a shift from C-alkylation in THF and alcohols to dominant O-alkylation in DMSO, DMF, and HMPA. This reflects the more dissociated and weakly solvated state of the enolate in the aprotic dipolar solvents.

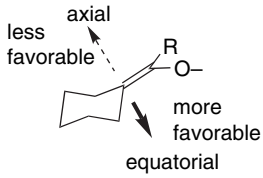
Another major influence on the C:O ratios is presumably the degree of aggregation. The reactivity at oxygen should be enhanced by dissociation since the electron density is less tightly associated with the cation. With the lithium enolate of acetophenone, for example, C-alkylation is the major product with methyl iodide but C-alkylation and O-alkylation occur to approximately equal extents with dimethyl sulfate. The C:O ratio is shifted more to O-alkylation by addition of HMPA or other cation-complexing agents. Thus, with four equivalents of HMPA the C:O ratio for methyl iodide drops from more than 200:1 to 10:1, whereas with dimethyl sulfate the C:O ratio changes from 1.2:1 to 0.2:1 when HMPA is added.[95]

Steric and stereoelectronic effects control the direction of approach of an electrophile to the enolate. Electrophiles approach from the side of the enolate that is less hindered. Many examples of such effects have been observed.[96] In ketone and ester enolates that are exocyclic to a conformationally biased cyclohexane ring there is a small preference for the electrophile to approach from the equatorial

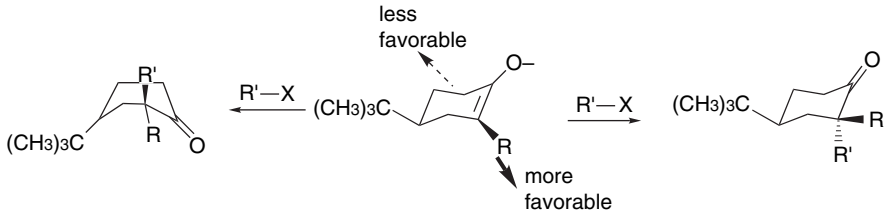
[95] L. M. Jackman and B. C. Lange, *J. Am. Chem. Soc.*, **103**, 4494 (1981).

[96] Reviews: D. A. Evans, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., Academic Press, New York, 1984, Chap. 1; D. Caine, in *Carbon-Carbon Bond Formation*, R. L. Augustine, ed., Marcel Dekker, New York, 1979.

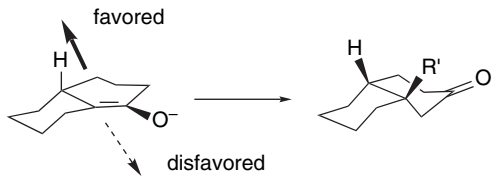
direction.[97] If the axial face is further hindered by the addition of a substituent, the selectivity is increased.



Endocyclic cyclohexanone enolates with 2-alkyl groups show a small preference (1:1–5:1) for approach of the electrophile from the direction that permits maintenance of the chair conformation.[98]



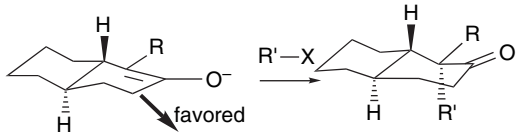
The 1(9)-enolate of 1-decalone exhibits a preference for alkylation to form a *cis* ring juncture.



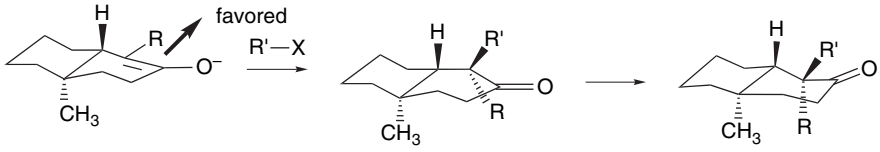
This is the result of a steric differentiation with of the electrophile approaching from the side of the enolate occupied by the smaller hydrogen, rather than the ring methylene group at the C(10) position.

The 2(1)-enolate of *trans*-2-decalone is preferentially alkylated by an axial approach of the electrophile. The stereoselectivity is enhanced if there is an alkyl substituent at C(1). The factors operating in this case are similar to those described for 4-*t*-butylcyclohexanone. The *trans*-decalone framework is conformationally rigid. Axial attack from the lower face leads directly to the chair conformation of the product. The 1-alkyl group enhances this stereoselectivity because a steric interaction with the solvated enolate oxygen distorts the enolate in such a way as to favor the axial attack.[99]

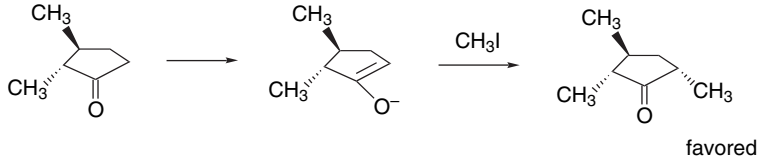
97. A. P. Krapcho and E. A. Dundulis, *J. Org. Chem.*, **45**, 3236 (1980); H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).
98. H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968); H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 1000 (1973); J. M. Conia and P. Briet, *Bull. Soc. Chim. France*, 3881, 3886 (1966); C. Djerassi, J. Burakevich, J. W. Chamberlin, D. Elad, T. Toda, and G. Stork, *J. Am. Chem. Soc.*, **86**, 465 (1964); C. Agami, J. Levisalles, and B. Lo Cicero, *Tetrahedron*, **35**, 961 (1979).
99. R. S. Mathews, S. S. Grigenti, and E. A. Folkers, *J. Chem. Soc., Chem. Commun.*, 708 (1970); P. Lansbury and G. E. DuBois, *Tetrahedron Lett.*, 3305 (1972).



The placement of an axial methyl group at C(10) in a 2(1)-decalone enolate introduces a 1,3-diaxial interaction with the approaching electrophile. The preferred alkylation product results from approach on the other side of the enolate.

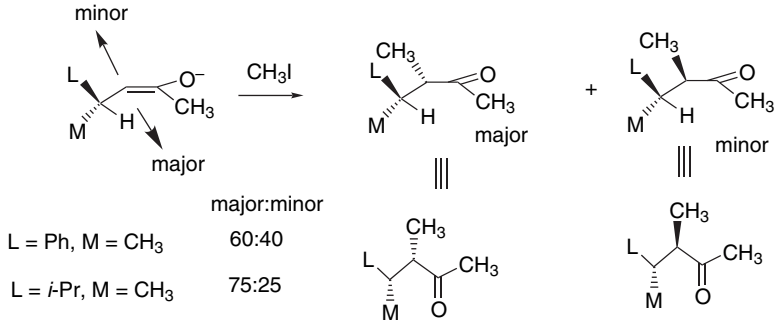


Houk and co-workers have emphasized the role of torsional effects in the stereoselectivity of enolate alkylation.[100] This analysis can explain the preference for C(5)-alkylation *syn* to the 2-methyl group in *trans*-2,3-dimethylcyclopentanone.



The *syn* TS is favored by about 1 kcal/mol, owing to reduced eclipsing, as illustrated in Figure 6.5. An experimental study using the kinetic enolate of 3-(*t*-butyl)-2-methylcyclopentanone in an alkylation reaction with benzyl iodide gave an 85:15 preference for the predicted *cis*-2,5-dimethyl derivative.

In acyclic systems, the enolate conformation comes into play. In unfunctionalized systems, alkylation usually takes place *anti* to the larger substituent, but with rather modest stereoselectivity.



Ref. 101

100. K. Ando, N. S. Green, Y. Li, and K. N. Houk, *J. Am. Chem. Soc.*, **121**, 5334 (1999).
101. I. Fleming and J. J. Lewis, *J. Chem. Soc., Perkin Trans. 1*, 3257 (1992).

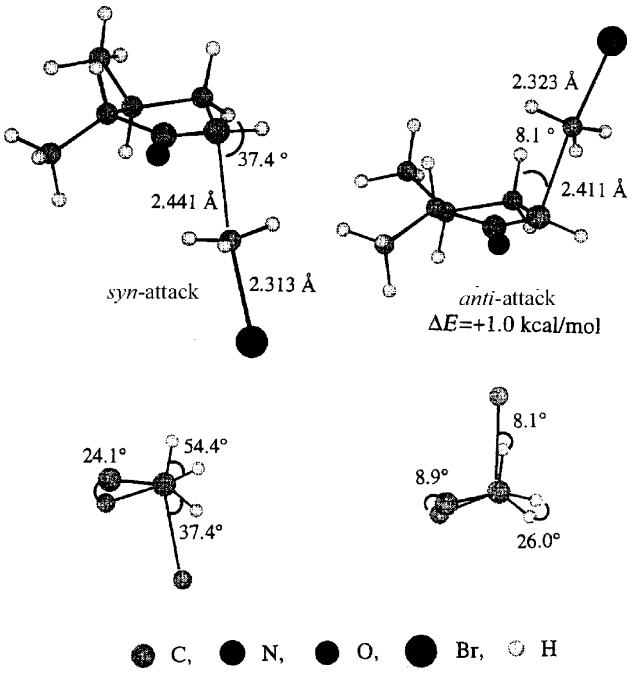
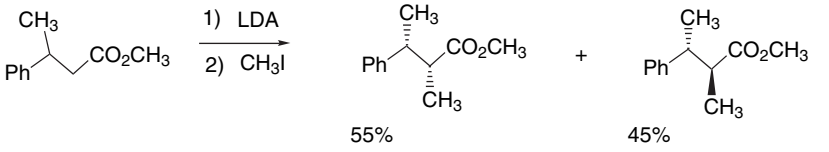
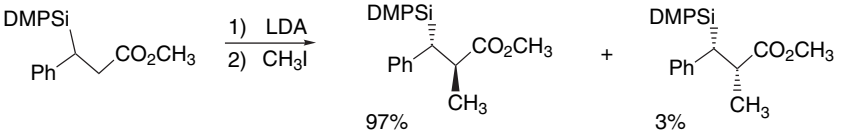


Fig. 6.5. Transition structures for *syn* and *anti* attack on the kinetic enolate of *trans*-2,3-dimethylcyclopentanone showing the staggered versus eclipsed nature of the newly forming bond. Reproduced from *J. Am. Chem. Soc.*, **121**, 5334 (1999), by permission of the American Chemical Society.

The enolate of the corresponding methyl ester gives a similar result.



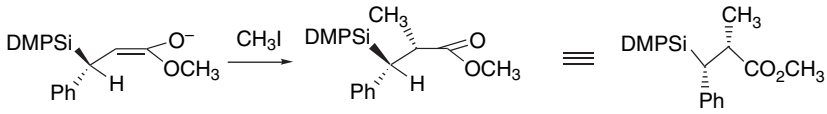
When a silyl substituent is present, the reaction becomes much more selective.



Ref. 102

[102] R. A. N. C. Crump, I. Fleming, J. H. M. Hill, D. Parker, N. L. Reddy, and D. Waterson, *J. Chem. Soc., Perkin Trans. 2*, 3277 (1992).

This result is due to a dominant steric effect of the large silyl substituent.[103]



In general, the stereoselectivity of enolate alkylation can be predicted and interpreted on the basis of the stereoelectronic requirement for an approximately perpendicular approach to the enolate with minimal torsional strain in combination and preference between the two faces on the basis of steric factors.

General References

E. Buncel, *Carbanions: Mechanistic and Isotopic Aspects*, Elsevier, Amsterdam, 1975.
E. Buncel and T. Durst, eds., *Comprehensive Carbanion Chemistry*, Elsevier, New York, 1981.
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E. M. Kaiser and D. W. Slocum, in *Organic Reactive Intermediates*, S. P. McManus. ed., Academic Press, New York, 1973, Chap. 5.
Z. Rappoport, ed., *The Chemistry of Enols*, Wiley, New York, 1990.
M. Szwarc, *Ions and Ion Pairs in Organic Reactions*, Wiley, New York, 1972.
J. Toullec, *Adv. Phys. Org. Chem.*, **18**, 1 (1982).

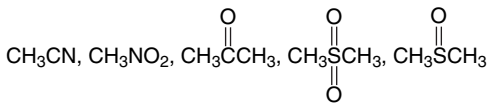
Problems

(*References for these problems will be found on page 1161.*)

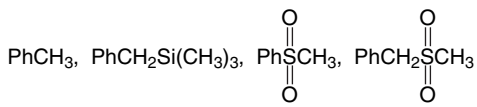
6.1. Predict the order of increasing thermodynamic acidity in each series of compounds and explain the basis of your prediction.

a. benzene, 1,4-cyclohexadiene, cyclopentadiene, cyclohexane

b.

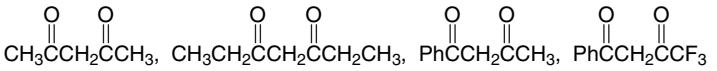


c.



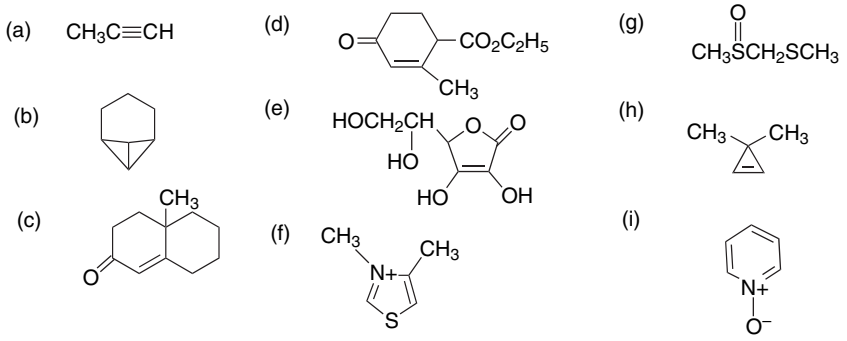
[103.] I Fleming, *J. Chem. Soc., Perkin Trans. 1*, 3363 (1992).

d.



e. 9-(*m*-chlorophenyl)fluorene, 9-(*p*-methoxyphenyl)fluorene, 9-phenylfluorene, 9-(*m*-methoxyphenyl)fluorene, 9-(*p*-methylphenyl)fluorene.

6.2. Indicate the most acidic hydrogen in each of the following molecules. Explain your reasoning.

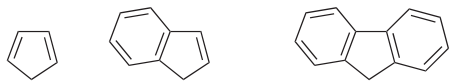


6.3. Offer an explanation for the following observations.

a. Base-catalyzed exchange rates indicate that the hydrocarbon cubane is much more acidic than cyclobutane, and even more acidic than cyclopropane.

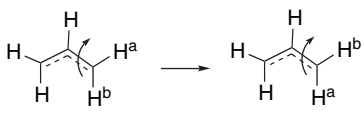
b. Cyclopropyl phenyl ketone (pK = 28.2) is less acidic than acetophenone (pK = 24.7) and undergoes C–H exchange more slowly than phenyl *i*-propyl ketone, despite the fact that its most acidic hydrogen is located on a cyclopropyl ring.

c. The order of acidity for cyclopentadiene, indene, and fluorene in DMSO is indicated below. The gas phase acidity is in the opposite direction, as measured by the proton affinity. Why does the fusion of benzene rings *decrease* the solution acidity relative to cyclopentadiene?



pK_{DMSO}	18.0	20.1	22.6
PA_{gas}	347.8	344.6	343.9

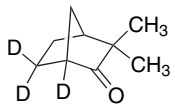
d. The rotational barrier of the allyl anion in THF, as measured by NMR, is dependent on the identity of the cation present.



M^+	$\Delta G^{\ddagger}$ (kcal/mol)
Li^+	10.7
K^+	16.7
Cs^+	18.0

6.4 a. The relative rates of hydroxide ion-catalyzed deuterium exchange at C(3) have been measured for bicyclo[2.1.1]hexan-2-one, bicyclo[2.2.1]heptan-2-one, and bicyclo[2.2.2]octan-2-one. What factor(s) could account for the much smaller rate of exchange for bicyclo[2.1.1]hexan-2-one?

b. Treatment of (+)-camphenilone with $K^+ \cdot {}^-O$-*t*-Bu in *t*-BuOD at 185°C results in incorporation of D, as indicated below. Racemization occurs at the same rate. Suggest a mechanism that could account for these observations.



6.5. Using data from Tables 6.1 (p. 580) and 6.2 (p. 583), estimate the extent of deprotonation for each hydrocarbon-base combination below. Discuss the uncertainties that could affect the calculation.

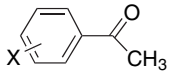
a. indene by 0.01 *M* $NaOCH_3$ in 1:1 DMSO-C_2H_5OH
b. fluorene by 0.01 *M* $NaOC_2H_5$ in 20:1 DMSO-C_2H_5OH
c. triphenylmethane by 5 *M* $KOCH_3$ in CH_3OH

6.6. The rates of removal of axial and equatorial protons from 4-*t*-butylcyclohexanone in NaOD/dioxane have been compared by an NMR technique. The rate of removal of an axial proton is 5.5 times faster than for an equatorial proton. How do you explain the difference?

6.7. The following table gives exchange rates in methanolic $NaOCH_3$ and pK values for some hydrocarbons. Determine if there is a correlation between the kinetic and thermodynamic acidity.

Compound	$k_{exchange}$ $M^{-1}s^{-1}(\times 10^4)$	pK
9-Phenylfluorene	173	18.5
Indene	50	19.9
3,4-Benzofluorene	90.3	19.75
1,2-Benzofluorene	31.9	20.3
2,3-Benzofluorene	2.15	23.5
Fluorene	3.95	22.7

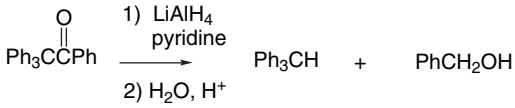
6.8. The acidity of various substituted acetophenones in DMSO is given below. Would you expect the ρ value to correlate best with σ, σ^+, or σ^-? Explain, considering each of the σ parameters explicitly. Do a plot of the pK/pK_0 values for each σ parameter.



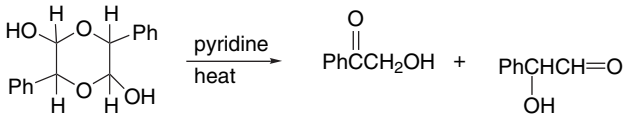
X	p*K*	X	p*K*	X	p*K*
p-$(CH_3)_2N$	27.48	H	24.70	*m*-Cl	23.18
p-CH_3O	25.70	*p*-F	24.45	*m*-Br	23.19
m-$(CH_3)_2N$	25.32	*m*-CH_3O	24.52	*m*-CF_3	22.76
p-CH_3	25.19	*p*-Br	23.81	*p*-CF_3	22.69
m-CH_3	24.95	*p*-Cl	23.78	*p*-CN	22.04
p-Ph	24.51	*m*-F	23.45		

6.9. Suggest mechanisms for the following reactions:

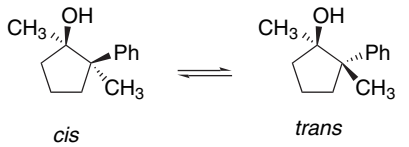
a.



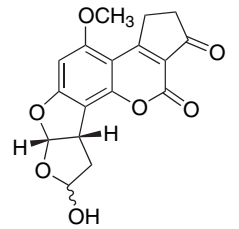
b.



c. Treatment of the *cis* and *trans* isomers of 1,2-dimethyl-2-phenylcyclopentanol with 0.25 *M* $NaCH_2SOCH_3$ in DMSO leads to an 72:28 equilibrium mixture favoring the *trans* isomer.

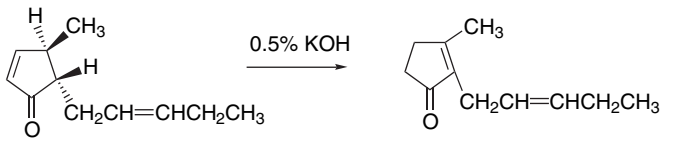


d. Aflatoxin B_1 hemiacetal racemizes readily in basic solution.

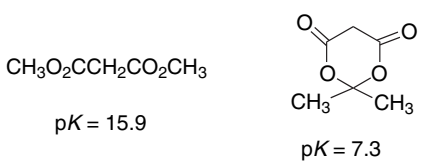


Aflatoxin B_1 hemiacetal

e. 4,5-Disubstituted cyclopent-2-enones can rearrange to 2,3-disubstituted cyclopent-2-enones in basic solution.

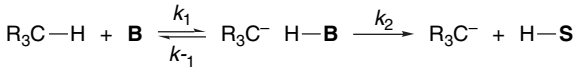


6.10. Meldrum's acid, pK = 7.3, is exceptionally acidic in comparison with acyclic analogs, such as dimethyl malonate (pK = 15.9). 5,5-Dimethyl-1,3-cyclohexadione is only moderately more acidic than pentane-2,4-dione. (pK = 11.2 versus 13.43). (All pK values in DMSO). It is found that the enhanced acidity of Meldrum's acid derivatives decreases as the ring size increases, with the larger ring compounds being similar in acidity to dimethyl malonate. Analyze the factors that contribute to the enhanced acidity of Meldrum's acid.



	pK
n = 5	13.0
n = 8	15.2
n = 12	15.1

6.11. In some solvents, such as $K^{+}\cdot{}^{-}$OR-DMSO, it can be shown that the *internal return* equilibrium characterized by k_1/k_{-1} is fast relative to the dissociation process characterized by k_2. In this process, the base returns the proton to the carbanion faster than the proton donor exchanges with other molecules from solution. If internal return is important under a given set of conditions, how might that affect the correlation between observed kinetic and thermodynamic acidity? How can the occurrence of internal return be detected experimentally?

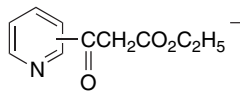


6.12. Discuss the following comparison of the enol content at equilibrium based on data given in Table 6.12. Discuss the reason for the differing enol content of the pairs of compounds in question.

a. Why does cyclohexanone have a somewhat higher enol content than cyclopentanone?
b. Why do methyl acetate and acetamide have much lower enol content than acetone?
c. Why does 2-indanone have a much higher enol content than 1-indanone?
d. Why does 5,5-dimethyl-1,3-cyclohexa-1,3-dione have a higher enol content than acyclic diones such as acetylacetone, even though intramolecular hydrogen bonding is not possible?

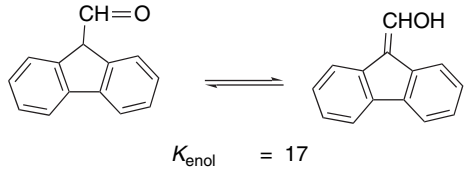
6.13. Identify the structural factors that lead to the special stabilization of the enol form noted in each example.

a. The enol content of the 2-isomer of 3-(x-pyridyl)-3-oxopropanoate esters is higher than for the 3- and 4-isomers.

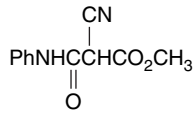


position	K_{enol}
2	0.86
3	0.15
4	0.19

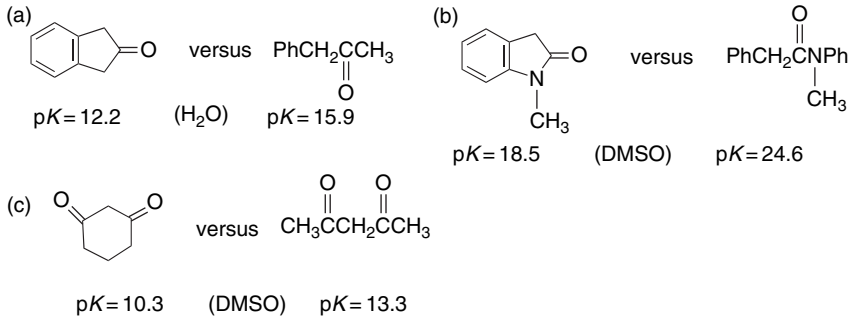
b. The K_{enol} of 9-formylfluorene is 17, that is, the enol form is favored at equilibrium.



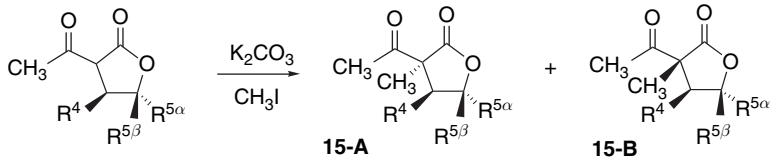
c. Monoanilides of 2-cyanopropane-1,3-dicarboxyate monoesters exist in an enolic form in the solid state and in halogenated solvents.



6.14. Certain cyclic compounds exhibit enhanced acidity relative to acyclic models. Offer an explanation for the examples given below.



6.15. The stereoselectivity of alkylation of 3-acetylbutyrolactones is influenced by alkyl substituents at C(4) and C(5). Analyze possible conformations of the enolate and develop an explanation of the observed stereoselectivity.

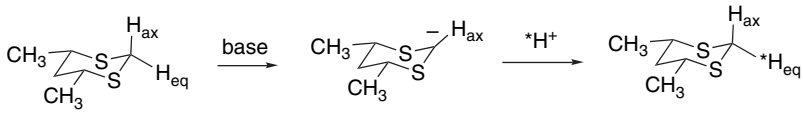


15-A **15-B**

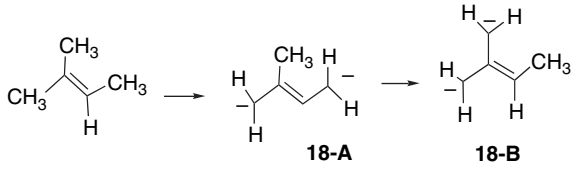
R^4	$R^{5\alpha}$	$R^{5\beta}$	**15-A:15-B**
CH_3	H	H	29:71
CH_3	H	*n*-Pr	<3:>97
CH_3	*n*-Pr	H	80:20
H	H	C_2H_5	25:75

6.16. Metal ions such as Zn^{2+}, Ni^{2+}, and Cu^{2+} enhance the rate of general base-catalyzed enolization of 2-acetylpyridine by a several orders of magnitude. Account for this effect.

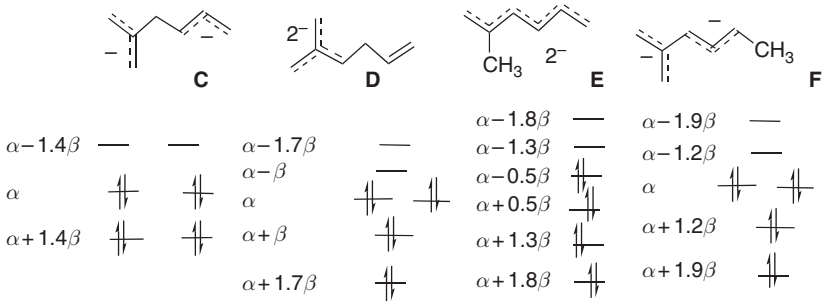
6.17. The C(2) equatorial hydrogen is selectively removed when 1,3-dithianes are deprotonated. Furthermore, if the resulting carbanion is protonated, there is a strong preference for equatorial protonation, even though it leads to the less stable axial orientation for the 2-substituent. Discuss the relevance of these observations to the structure of the sulfur-stabilized carbanion in MO terminology.



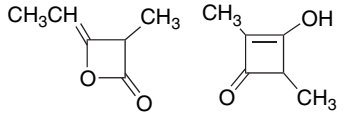
6.18. a. It is found that when 2-methyl-2-butene is converted to a dianion, it first gives the 2-methylbutadiene dianion **18-A**, but this is converted to the more stable anion **18-B**, which can be referred to as a "methyltrimethylenemethane dianion. Does simple HMO theory offer an explanation for this result?



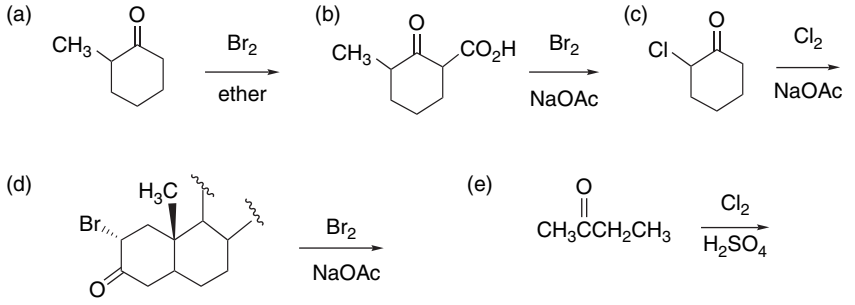
b. The HMO diagrams of several conceivable dianions that might be formed from double deprotonation of 2-methyl-1,5-hexadiene are given. On the basis of these diagrams, which dianion would be expected to be most stable?



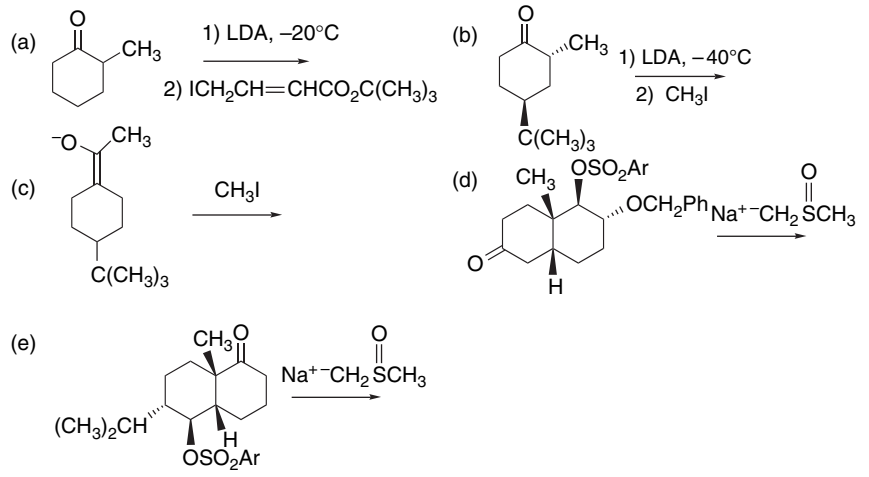
6.19. Which of the two possible structures for the dimer of methylketene is in best accord with the observed pK of 2.8? Explain.



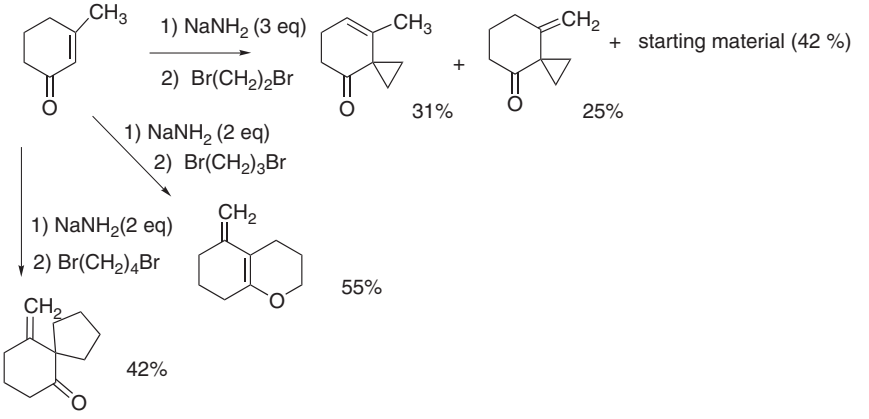
6.20. Predict the products of each of the following halogenation reactions.



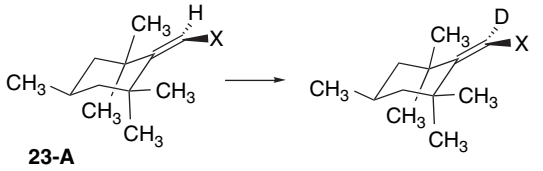
6.21. Predict the structure and stereochemistry of the products that would be obtained under the specified reaction conditions. Explain the basis of your prediction.



6.22. The alkylation of 3-methylcyclohex-2-enone with several dibromides led to the products shown below. Discuss the outcome of each reaction and suggest an explanation for the dependence of the product structure on the identity of the dihalide.

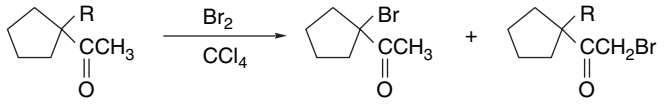


6.23. The stereochemistry of base-catalyzed deuterium exchange has been examined for **23-A**, where X = CN and COPh. When X = CN, the exchange occurs with 99% retention of configuration, but with X = COPh, only about 30% net retention is observed. Explain these contrasting results.



23-A

6.24. The distribution of α-bromoketones formed in the reaction of acetylcyclopentane with bromine shows an altered product ratio when the 1-position of the ring is deuterated. Assuming that acid-catalyzed enolization is the rate-determining step in bromination, calculate the primary isotope effect.

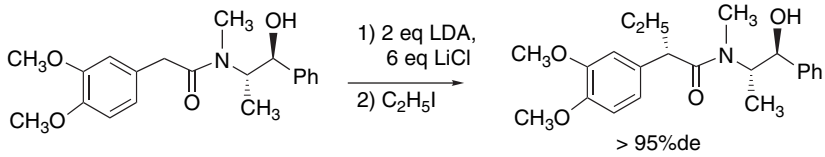


R = H	94%	6%
R = D	80%	20%

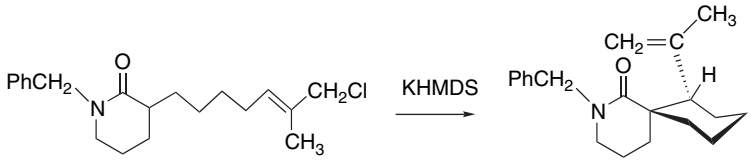
6.25. Analyze the mechanisms and transition structures for the following alkylation reactions in order to determine the factors that lead to the observed stereoselectivity.

a.

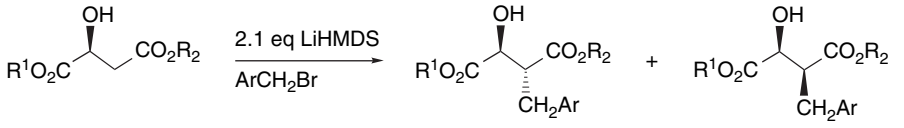
b.



c.



6.26. Several dialkyl malate esters were alkylated with a benzylic bromide. The dimethyl and diethyl esters show a 8:1 and 9:1 selectivity for **26-A** (*si* face, respectively). The diastereoselectivities are shown for several more bulky esters. Figure 6.P26 gives the HF/6-31G* structures of the corresponding enolates. Explain the observed stereoselectivity on the basis of structural features present in these enolates.



Ar = 4 – benzyloxy – 3 – methoxyphenyl **26-A** **26-B**

	R^1	R^2	**26-A:26-B**
1	*i*-Pr	*i*-Pr	19:1
2	*t*-Bu	*t*-Bu	7:1
3	*i*-Pr	*t*-Bu	4.5:1
4	*t*-Bu	*i*-Pr	40:1

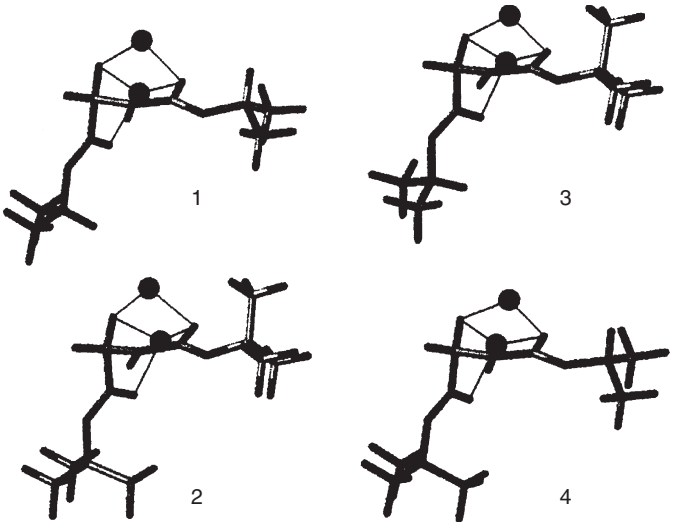


Fig. 6.P26. HF/6-31G* structures of enolates **1–4**. Reproduced from *Helv. Chim. Acta*, **85**, 4216 (2002), by permission of Wiley-VCH.